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Primary Biases in Twin Studies

A Review of Prenatal and Natal Difference-producing Factors in Monozygotic Pairs

BRONSON PRICE

Children's Bureau, Federal Security Agency, Washington 25, D.C.

1. INTRODUCTION

In all probability the net effect of most twin studies has been underestimation of the significance of heredity in the medical and behavior sciences.

This happens because twins are relied upon for crucial evidence regarding individuals who are not twins, and that reliance is unsound.

The crux of the twin method of studying heredity-environment problems is, in principle, sound enough. It is the assumption that monozygotic twins are "experiments" which nature has conducted for us, starting in each case with identical sets of genes and varying environmental factors.

However, we are after-the-fact observers of the results, and are left to guess what environmental factors nature put into the experiments. Where we judge those factors wrongly, we are likely to interpret the results wrongly so far as individuals who are not twins are concerned. And nature is, so to speak, all too "designing" in her experiments with twins. Indeed, she sometimes conducts them with real mischief so far as the twins are concerned—and almost as though to mislead us into minimizing her powers among nontwins.

There is, for example, at least one kind of environmental influence that is not only peculiar to the majority of monozygotic pairs but acts before they are born. Over 98% of humans have never been exposed to this condition at all. Yet its prenatal effects on the twins subjected to it are sometimes very severe, and the after-effects may cause most of the larger differences observed in monozygotic pairs postnatally. When this condition and certain other factors more or less unique to twins are overlooked in studying them, the intrapair differences are sometimes attributed to environmental influences that probably had little, if any, part in producing the differences.

As a result, twin studies are often interpreted as proving that heredity is not a factor of much significance, and as proving the special importance of a wide variety of environmental factors. These range from dietary supplements proposed for expectant mothers in the hope of preventing congenital defects in infants, to psychiatric treatments for repressed "hostility" as a supposed

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cause of cardiovascular disease. Such proposals tend to reflect the training or preconceptions of the authors reporting twin studies. Their inferences are often questionable because the environmental conditions affecting twins as "natural experiments" may be very different in kind from environmental factors which investigators assume to be significant in the pairs studied.

The problem is important for several reasons. There are, first, the twins themselves and their parents, who are done no service by misinterpretations on our part. Furthermore, there is the fact that inferences drawn from the reports of twin studies now in medical and other literature are daily affecting the diagnosis and treatment of a great variety of human maladies. Finally, there is the fact that, year after year, a considerable part of all research effort in medical genetics is spent upon the twin method, and often with less critical judgment than Galton exercised when, 75 years ago, he was the first to make systematic use of the method.

Views similar to those in this paper have been stated in a series of cautions expressed by other authors, beginning with Weismann's remarks (1893, p. 255). The present review attempts to supplement the earlier criticisms, and, so far as possible, to make the points more convincing by including a fair amount of background material. This would seem to be in order because the earlier criticisms have so often been ignored or discounted by subsequent investigators.

This review is not exhaustive or definitive, however. There is much room as well as need for further evaluation of the hundreds of twin studies published to date, particularly from the standpoints of embryology and physiological genetics. Moreover, no one could attempt to review what appear to be the errors of numerous other authors in this complex field without becoming the more conscious of his own likelihood of error in the same field. The reviewer hopes that his efforts will be corrected as necessary and built upon where possible in further examinations of the very large amount of material that is available.

2. SCOPE AND TERMINOLOGY

Popenoe (1922), Muller (1925), and Burks (1928) noted that postnatal environmental factors are not necessarily the same for monozygotic twins as for other individuals. Since 1930 this consideration has become widely accepted as a kind of bias operating in investigations of twins, excepting, of course, studies of pairs reared apart. Yet, with acceptance of the idea that this kind of bias may be serious, there has not been very complete agreement as to the direction of its effect so far as the twin method's purpose of illuminating heredity-environment problems in nontwins is concerned. Though most investigators assume the bias operates to overstate the importance of heredity among nontwins, a minority of investigators (e.g., Cronin, 1933) write as though intrapair rivalry and competition were often very intense in monozygotic twins, and as though such environmental factors cause individual differences in mono-

zygotic pairs to a greater extent than they cause (i.e., add to genetically determined) individual differences in dizygotic twins or siblings. Investigators making this point do not usually go on to note that it would, if valid, tend to make twin studies exaggerate the significance of environmental factors, and equally to underestimate the importance of heredity; yet that is the meaning of the point if any general statement can be made about it.

These postnatal biasing factors are mentioned here only to avoid confusion. They have received, oddly enough, far more attention than the much longer-known factors which are herein called *primary biases*, and which are defined (cf. §4, p. 301) as *prenatal and natal environmental factors peculiar in kind or degree to twins*. The reviewer does not assume that postnatal biases are unimportant in twin studies. He does hold that since all postnatal factors are secondary in the sequence of development, there is little chance of evaluating the postnatal biases properly until we have more certain knowledge than we now possess concerning the effects of primary biasing factors. For that reason this review neglects postnatal influences, except where it is necessary to consider the possibility that they may have been confounded with one or more of the primary biases. The reviewer doubts, however, that effects of primary and secondary factors are such as to cancel each other out, or that any modifications of the twin method which do not take full account of the primary biases can make that method generally valid.

Types of twins

Since data on twinning are studied for the information they can yield on many different kinds of problems, it seems desirable to note some further aspects of the subject which this review does not attempt to cover. Although the treatment concerns what happens in the months following the formation of twin zygotes, it does not deal with what may occur just before and during that stage. Problems of the inheritance or other causes of twinning are noted only incidentally; their solution would not, by itself, particularly affect the twin method as it is now known and used.

There is reason to think that those deviations in ordinary human zygote formation which result in very early twin embryos of some kind or degree are considerably more frequent than the data from birth certificates would indicate. For this and other reasons few problems are of more interest, and perhaps of more significance for eventual understanding of the usual process of human zygote formation, than the processes by which human twin zygotes are formed.

Concerning the nature of the latter processes, however, we appear to be more in the dark than is sometimes assumed. We know more, but not much more, than was known in Galton's time. The comparative findings on other animals have not proved conclusive, and indeed they seem to have been misleading almost as often as they have been instructive for human data. Of the numerous theories so far offered to account for specifically human twinning, it appears that few can yet be excluded with much finality.

Much has been established, nevertheless, concerning those stages of embryonic and fetal development which represent the more or less immediate consequences of twin zygote formation. It is this knowledge, including especially the findings of Friedrich Schatz, that the present review tries to relate to the twin method of studying nature-nurture problems.

The facts known to date concerning the kinds of pairs that result from human twinning processes are summarized below, together with definitions of the terms to be used herein for the three main types of pairs. These terms are not thought suitable, necessarily, for general purposes. They have been chosen for this review because the discussion is made easier through use of the shortest words consistent with earlier terminologies, some of which have reflected the winding course of the history of our knowledge more than they have essential facts.

From indirect somatologic and serologic observations (and despite the lack of direct cytological evidence in humans) we may believe that there are, at least in the main, two genetic types of twins, the *monozygotic* and *dizygotic*. For these the abbreviations "MZ" and "DZ", respectively, will be used.

From embryological and obstetrical data it has long been known that there are two types of twin secundines or chorio-placental structures. For the double and single conditions of these structures the terms *dichorial* and *monochorial* will be used. (The existence of monoamniotic cases is well known also, and they are not particularly rare, but they are properly regarded as a subgroup within the monochorial type.)

The relation between these two sets of observations is complicated by the fact that a few MZ pairs are dichorial. To designate them separately from the more common types it is essential to specify both the type of secundines and the genetic type, i.e., as 'dichorial-MZ'. For the other two types, the monochorial (MZ) and (dichorial) DZ, the parenthesized parts of the designations are omitted in this review, on the working hypotheses that all monochorial pairs are MZ and that all DZ pairs are dichorial. These assumptions probably hold even though the converse statements are false (that all MZ pairs are monochorial or all dichorial are DZ). The frequency of dichorial-MZ pairs and the differentiation of the three types are discussed in section 3.

It is not ordinarily known, of course, which pairs are monochorial and which are dichorial-MZ, so it is often necessary to use the term 'MZ' alone. Especially when the twins so designated are a sizable group for whom data on secundines are lacking, it is to be remembered that some dichorial-MZ cases are probably included. Similarly, when the term 'dichorial' is used alone (e.g., for pairs known only from records of their secundines), it is to be assumed that some dichorial-MZ cases may be included unless the zygosity of the pairs is known on other grounds. To save repetition, the word 'twin' will often be omitted in connection with all such terms, though 'nontwins' will be specified where necessary to distinguish them as such.

Twin-control work

In concluding this section the reviewer wishes to stress that there is one important kind of research with twins which is not significantly affected by the problems to be discussed. That is "twin-control" testing, as used, for example, in comparing the merits of one medical treatment or teaching method with another. The procedure dates from 1905, when Walcher and Elsässer so arranged that one member of a pair of twin infants of monochorial type was kept lying on his side most of the time, while the cotwin was kept lying on his back, in order to test the effects of these positions on the infants' head shapes. An example of modern application of the procedure is the study by Robertson *et al.* (1947), who tested the effects of thiamine supplements on growth, vision, and learning with a large number of MZ pairs.

Unfortunately, this type of research with twins has been associated too loosely with the classical twin method. Twin-control work is an efficient method of measuring the effects of certain environmental factors. By itself, the procedure does not involve assumptions about, or necessarily yield information on, the origin of the medical, psychological, or other function with which one may be dealing. If each member of several MZ pairs had tuberculosis, for example, and were employed for studying different treatments of that disease, the experiment would be equally efficient whether one supposed tuberculosis to be conditioned mainly by environmental or genetic factors. Nevertheless, the twin-control procedure is a fully experimental one, because the experimenter knows both the circumstances at the start of the experiment and what goes into it.

The procedure does not, as some have thought, differ essentially from biometric methods, but is rather a biometric method in the best sense. For the point is to take fullest advantage of the correlation term in significance-of-difference formulas, and so to reduce the number of cases needed for a crucial test. In marked contrast to nature-nurture twin studies, twin-control work should involve deliberate selection of the most similar MZ pairs available.

This is sometimes carried so far as to suppose that the members of each MZ pair employed for the work need to be exactly similar. That is hardly correct, even though it is true that the test's efficiency is improved by careful selection of the pairs. Yet, an essential part of the method is measurement of the status of each individual twin, prior to the start of the experiment, in the functions concerned, so that allowance can be made as necessary for any pre-existing intrapair difference. (As will be noted in section 8, absence of this feature is, in the writer's view, a good reason for doubting that the famous studies of reared-apart pairs are comparable to twin-control experiments).

As indicated in section 4, the special prenatal handicaps of monochorial pairs almost certainly mean that greater average differences occur in them than in dichorial-MZ pairs. This does not necessarily mean that monochorial pairs should be excluded from twin-control tests. One needs only to exclude from such work the least similar third or perhaps half of all MZ pairs. Then, for the remaining half or two thirds, the initial intrapair correlations will be higher than those obtainable by matching unrelated individuals, or even by choosing the more similar pairs from among DZ twins or siblings. For this reason the use of selected MZ

pairs in twin-control work will probably remain the most efficient testing procedure available for human research for a long time to come.

However, for tests conducted over a long period of time, it might indeed be well to restrict the work to selected pairs of dichorial-MZ type so far as possible, since in monochorial cases there is more chance that a latent effect of prenatal factors might begin to show up in an individual twin only after the test was well along. The possibility of erroneous results from this source cannot be dismissed where the testing is protracted and only two or three pairs are used. But the risk can be reduced by employing a considerable number of pairs, and watching each individual for any unusual development not readily attributable to the treatment being tested and not occurring in the other individuals receiving the same treatment.

As this review is concerned to some extent with hospital recording of twin births according to type of secundines, a practical consideration for future twin-control work may be mentioned. In this country, as compared with most others, the proportion of births occurring in hospitals has long been relatively high. Moreover, the percentage has risen from about 35 per cent in 1935 to over 85 per cent in 1950. Concurrently, the better maternity and general hospitals have been improving their records of twin deliveries, and the records frequently state whether the secundines were monochorial or dichorial.

As matters have stood heretofore, for only a small minority of MZ pairs could information be obtained from the twins, their parents, or even the physician who attended their birth as to whether the secundines were monochorial or dichorial. But it is now often possible, at least for younger MZ pairs, to learn from their parents or from their birth certificates what hospitals they were born in, and to obtain information from the hospitals as to whether the twins were monochorial or dichorial. The hospitals need only be furnished with the dates of the twins' birth and the names of their parents. For future work, therefore, it should be possible to distinguish increasing numbers of dichorial-MZ twins reliably enough for purposes of twin-control studies. It is true that the secundines of some dichorial-MZ cases are "fused" to a considerable extent, and in some cases a pair of that type will be reported mistakenly as monochorial. Such errors would not be of consequence, however, where one's object was the selection of pairs that were assuredly of dichorial-MZ type.

3. FREQUENCY AND DIFFERENTIATION OF THE TYPES OF TWINS

For purposes of the next section it is important to have, as background information, some estimate of the birth rate of dichorial-MZ pairs. For reasons of long standing the statistical information about that rate is not very satisfactory. The difficulties in estimating the rate, and the nature of such information as we have concerning it, will be clear from a brief review of the history of the problem.

In the 1870's the "one-egg" origin of monochorial twins was generally known, thanks to H. Meckel (1850), Schultze (1854, 1856), and Kleinwächter's excellent review (1871). In the light of that knowledge and the fact that MZ

pairs are always of the same sex, Louis-Adolphe Bertillon (1874) was the first to develop the statistical device now known as "Weinberg's rule," whereby the number of MZ pairs is accurately estimated by subtracting twice the number of opposite-sex pairs from the total number of pairs. It is of incidental interest that Galton (1875*b*) knew of this rule; he cited "Mr. C. Ansell" as his informant. (Ansell might have read of it in Bertillon's article, but it would seem at least as likely that he thought of the rule independently, considering the number of authors who have since done so.)

In line with the accepted theory of his time, Bertillon thought that if all monochorial pairs were MZ, so all MZ pairs might be monochorial. But, to check the frequency of MZ twins given by the rule, he asked obstetricians how often they had noticed monochorial cases. The frequency indicated by their reports was much lower than the rule had led him to expect. Bertillon therefore concluded that whatever cause produced monochorial cases was not sufficient to account for the excess of same-sex pairs which he had observed.

Hensen (1881) also found a discrepancy in the same direction between the frequency given by the rule and the frequency of monochorial pairs reported by obstetricians. However, it was not until Weinberg (1901) re-examined the problem that the discrepancy received much attention. Weinberg found that the rule showed the frequency of MZ twins to be "twice" their frequency as given by the obstetricians.

This stimulated much further study of the question during the next 15 years. Weinberg agreed that his word "twice" may have exaggerated the facts; but, to his credit, he maintained that the discrepancy was real and not attributable to some kind or kinds of error. All other students of twins and twinning attempted to explain away the facts, and their efforts were all too successful. The opinion that the discrepancy was not a significant one became incorporated in most of the reference works that are considered authoritative today.

No one appears to have stated what the facts meant until Danforth (1916) took up the question. Suspecting that some MZ pairs were dichorial, he consulted physicians who had attended plural births. He did not find a dichorial-MZ pair, but, even better, he found a set of triplet children who were clearly MZ, and whose attending physician was certain that their secundines had been trichorial. Danforth held it "very probable" that the discrepancy between Weinberg's rule and obstetrical findings "represents the number of cases in which uniovular twins develop in separate sets of fetal membranes."

Some years later Siemens (1925*a*, *b*) published the facts concerning six dichorial-MZ pairs that he had found. Several further studies were then undertaken. Essen-Möller (1941*a*) was able to add 61 MZ pairs of his own to the 129 which had been reported by Curtius (1930), Lassen (1931), Steiner (1935), and Voûte (1936). Out of the total of 190 MZ pairs, 63, or 33%, proved to be of dichorial-MZ type. This finding is consistent with, but more certain

than, the data in the earlier studies showing discrepancies between Weinberg's rule and obstetrical reports. We may now use Essen-Möller's result, together with data from studies of registration data, to estimate the birth rate of dichorial-MZ pairs per 10,000 deliveries.

Applying Weinberg's rule to data on registered births, numerous authors have reported on the birth rate of the two types of MZ pairs taken together. This total MZ rate is found to be approximately 40 pairs per 10,000 registered deliveries when pairs with one or both twins stillborn are included. It shows some variation with race and maternal age (Strandskov and Edelen, 1946; Stern and Enders, 1948), but this variation is small and some of it may be due to "registration phenomena," as Dahlberg pointed out in 1926. In contrast, the DZ rate shows marked variation with race and maternal age (Weinberg, 1901, and numerous other authors). We need only note that the DZ rate in the United States is roughly twice the total MZ rate.

For the total MZ rate with stillbirths excluded we may use the data of Yerushalmy and Sheerar (1940), who have worked out the figures for the United States covering the five-year period 1931–1935. Weinberg's rule showed that 35,760 both-living MZ pairs were born in that period, during which all deliveries, single and plural, totaled 10,853,459. These figures yield the rate of 33 both-living MZ pairs per 10,000 deliveries.

Use of the factor of 33% obtained from Essen-Möller's compilation would give 11 per 10,000 deliveries for the birth rate of dichorial-MZ pairs in which both twins are born alive. However, this method of estimating the rate assumes that mortality following birth is the same for both types of MZ pairs. If it is not, and if the monochorial cases are subject to comparatively higher mortality the birth rate of dichorial-MZ cases must be lower than the figure just derived. We may estimate, conservatively, that the rate is about 8 pairs per 10,000 deliveries.

It is to be hoped that this rate will be checked from available hospital records. It would be necessary to select data from hospitals where care has been taken in examining the secundines, recording the sexes of the infants, and reporting on total deliveries. Since numerous hospitals have been collecting such information for a decade or two, it ought to be possible to assemble data on 50,000 or more deliveries, and to use Bertillon's method to estimate the dichorial-MZ rate directly.

Differentiation of the three types. The reviewer does not assume that vascular anastomoses between the placentas of dichorial pairs never occur, nor is it thought that we can yet be sure that aberrant genetic types of twins never arise. In the light of the data so far accumulated, however, it is believed safe to assume that if there are kinds of twins other than, or "intermediate" among, the three types already named, their frequencies are sufficiently low that they would seldom complicate work of the kind to be discussed.

It is assumed (*a*) that vascular connections having serious consequences for twins occur only in the placentas of monochorial fetuses, and (*b*) that, at birth, the monochorial cases can

be differentiated from those that are dichorial (MZ or DZ) through expert examination of the secundines. Assumption (*b*) might prove to be imperfect, but it is based on the findings of practically all of the investigators who have studied the problem in the past century. These investigators include those who are not necessarily committed concerning assumption (*a*), which is discussed at the end of this section. In cases where inspection leaves substantial doubt about the type of secundines, "expert examination" as used here means methods of injecting the placental vessels, stereo-X-ray study, and microscopic examination of the septa as recommended by Kiffner (1929), Steiner (1935), and Wenner (1947).

It is also assumed that after the monochorial and dichorial cases have been differentiated by examination of the secundines, the dichorial-MZ and DZ pairs can be differentiated by serologic tests shortly after delivery, or by Siemens' "similarity method" within six months following birth (Lassen, 1931). The use of blood tests as an aid in diagnosing zygosity began with the work of Schiff and von Verschuer in 1931, and was further developed by Rife (1933*a*, 1938*b*), Levit and Soboleva (1935), Wiener and Leff (1940), and Dahr (1941). With the ABO, MN and Rh-Hr types alone, approximately 80% of all DZ pairs can be distinguished from MZ, and with the discovery of new antigenic factors we may anticipate a time when doubtful zygosity will cease to be a significant problem (Cotterman, personal communication, 1946).

As regards assumption (*a*) above, vessels of one type or another passing between the placentas of occasional dichorial cases have been observed by Kadjar (1927), Scipiades and Burg (1930), Lassen (1931), Tüscher (1936), Szendi (1936, 1938*b*), and Pérez, Firpo, and Baldi (1947). None of these investigators have claimed that the vessels they found were such as to make expert differentiation between any dichorial case and monochorial cases impossible or even difficult. There remain, however, two questions: the frequency of dichorial cases showing anastomoses among all dichorial cases; and whether such anastomoses as do occur in some dichorial cases are analogous in structure or physiological effects to the vascular connections in monochorial cases.

No one appears to have tried to compile a frequency figure. The reviewer will not attempt to do so either, but will note that if the six collections cited above are considered together with other carefully studied collections where absence of such anastomoses has been reported, the frequency would seem to be quite low.

As to whether anastomoses in some dichorial cases have effects analogous to those in monochorial cases, the best indication known to the reviewer is found in the marmoset, which is the only primate that reproduces by bearing DZ twins regularly. According to Wislocki (1939) the adjacent chorionic walls of marmoset twin embryos break down at an early stage. The twins not only develop in one chorion, but there are usually extensive vessel connections between the two placental discs. Yet no "freemartin" effects (discussed in section 8) in opposite-sex pairs of these twins, or other untoward consequences in either same-sex or opposite-sex cases, have been found by the investigators who have studied them to date.

This fact does not prove that vascular connections between human dichorial cases have little or no consequences, but is consistent with that supposition. As will be brought out in section 6, the reason for the effects of vascular connections in monochorial cases lies in the vessel arrangements peculiar to those cases; and, except as connections in some dichorial cases might develop in the same way, one would not anticipate the same consequences in dichorial pairs.

4. NATURE OF THE BIASES AND NEEDED WORK

The chief kinds of primary bias known or presumed to affect the twin method may be termed *natal factors*, *lateral inversions*, and *effects of the mutual circulation*. Pairs of DZ type are affected by the natal factors and to some extent

by lateral inversions, but since most of the biasing influences arise in connection with MZ pairs it hardly seems necessary to go beyond discussion of the problem in pairs of the two MZ types.

Let us first distinguish among the biases as well as we can in the light of the indications now available, after which possible ways of judging separate effects of these factors in the two MZ types will be discussed.

Natal factors

Whether or not they introduce as much bias into studies of mature twins as has sometimes been thought, the earliest recognized class of biasing factors comprises the special conditions of placentation, position *in utero*, crowding, and delivery, to which all twins are subject before birth. If these factors do not differ in kind, they surely differ in degree from the analogous conditions for nontwin individuals.

The factor of placentation (including differential nutrition of the fetuses that might be associated with it) may be important during early as well as late stages of twins' gestation. But to the extent that crowding and intrauterine position are important at all, they are probably not important until the last few weeks before delivery. The circumstances of delivery are probably more important than any of the conditions just noted. It would seem possible, though admittedly arbitrary, to group the factors of placentation, position, and crowding together with the conditions of delivery, and to use the term 'natal factors' for this whole group of special environmental conditions that are more or less peculiar to twins.

In work of the kind to be sketched later, some consideration might have to be given to the comparatively short gestation period that is known to be fairly typical of monochorial pairs. However, the net result of the difference between monochorial and dichorial pairs in average gestation period is probably small, inasmuch as some obstetrical findings suggest advantages as well as disadvantages, so far as conditions of *delivery* are concerned, for *twin* pairs born prematurely. It should be noted also that the study would, necessarily, be concerned with those pairs in which both individuals survive infancy. Since both twins of markedly premature pairs probably do not survive as often as pairs born after eight months gestation, possible differential effects of natal factors as between monochorial and dichorial pairs would not appear very important in follow-up studies.

It would be difficult to say when the importance of natal factors as a source of bias in twin studies was first noted, because the factors peculiar to twin deliveries have been discussed by obstetricians for a very long time. However, special importance has been assigned to the natal factors as a source of bias by Rosanoff and his colleagues (1934–37), as well as by Brander (1935–40). As some evidence to the contrary, there are the findings of Gardner and Newman (1944). Since quadruplets should be affected more than twin pairs by the natal factors, and since the effects of natal factors alone should be well reflected in "four-egg"

sets, Gardner and Newman have given special attention to the question in studying such sets. While the investigators do not offer their findings as conclusive, they report no clear evidence of the effects of natal factors in any of the three sets of tetrazygotic quadruplets whose histories they have been able to study so far.

Benda (1945) has not been concerned with twin deliveries, but has called for "an adequate research method" to test the meaning of the moderate statistical association which he and numerous other investigators have found between difficult labor and delivery on the one hand, and, on the other, the incidence of mental deficiency in the surviving offspring. In the deliveries of 50 dichorial-MZ pairs there would almost certainly be several instances where labor and delivery were more difficult in the case of one twin than in the case of the other. Data obtained by following up such pairs may be imperfect from a "twin-control" viewpoint, but would appear to have at least as much value as further work on the problem of birth injury along the lines of the large scale studies already reported in the literature.

Lateral inversions

The term 'lateral inversions' is used for all degrees of "asymmetry reversal" observed in twins' physical structures, from complete *situs inversus viscerum* through various degrees of transverse situs to ordinary "mirror-imaging" of skin and hair patterns.

One might, perhaps, expect significant lateral inversions to occur less often in dichorial-MZ twins than in monochorial pairs. It is believed (Newman, 1916; Morrill, 1919) that scission of the embryo disturbs the normal development of asymmetry; when scission is relatively late there is less chance for complete recovery of normal or genotypical asymmetry, with the result that lateral inversions are more likely to arise. Scission occurs much earlier in dichorial-MZ pairs than in monochorial pairs, as otherwise the former pairs could not develop two sets of chorio-placental structures. Supposedly, then, the dichorial-MZ pairs should show relatively few lateral inversions.

Apparently the question as to whether this theoretical expectation is confirmed in fact has not been given much attention as yet. There is every reason to believe that scission usually occurs later in conjoined pairs (which are always monochorial) than it does in ordinary or "separated" monochorial pairs; and, as is well known, the conjoined pairs show the most marked degrees of lateral inversion. While this is consistent with the general theory, it scarcely proves that dichorial-MZ pairs showing marked lateral inversions are infrequent.

Accordingly the writer has watched for reports of dichorial-MZ pairs showing significant differences due to lateral inversions, and has found two such cases. In the pair reported by Cockayne (1939) one twin showed complete transposition of the viscera and was right-handed, while the other twin was normal except for left-handedness. The pair were clearly MZ and it was believed that there had been two placentas at the twins' birth. In another pair reported by Renssen (1942), hospital records showed that the boys were of dichorial-MZ type beyond any doubt. One twin showed a clearly developed ocular ptosis which was present in the other twin to only a "small degree." Since the father showed the trait also, and since the insufficiency of the rectus muscle that is typical of the syndrome was similar in the father and in the more markedly affected twin, Renssen concluded that the dissimilar expression

of the trait in the twin pair was an effect of lateral inversion. He noted that, in general, the manifestation of ocular ptosis is very variable.

We cannot be certain that Cockayne's pair was dichorial, and an alternative explanation is possible for Renssen's case. For there might have been, genotypically, "threshold" manifestation of ptosis in both twins, and the marked insufficiency of the rectus muscle in the one twin could, conceivably, have arisen from birth injury to that twin.

While Renssen's explanation would appear more plausible than the one in terms of birth injury, the latter possibility is mentioned by way of noting that significant effects of lateral inversions, or at least functional effects of them, are sometimes open to doubt. An *experimentum crucis* may never be found, but one may hope that further studies of lateral inversions, especially in dichorial-MZ pairs, will throw much light on the problem.

Although there seems to have been little discussion of the relative frequencies of lateral inversions in dichorial-MZ and monochorial pairs, the literature on the general problem of lateral inversions is very extensive. Among the outstanding reviews are those by Newman (1917, 1923, and 1940*a*), Danforth (1919*a*, 1924), Dahlberg (1926, 1943, and 1948), and Rife (1933*b*, 1940, 1950).

Considering these and numerous other valuable contributions to the subject, it appears to the present writer that the obviousness of lateral reversals may have led to some exaggeration of their effectiveness as causes of important differences in twins. Various authors (e.g., Newman, Freeman, and Holzinger, 1937) have noted that the clear physical differences occasioned in MZ pairs by lateral inversions do not necessarily mean that those differences have a corresponding functional significance to the individual twins. We may grant that lateral inversions are very important in studies of handedness, handwriting, and analogous variables, and that the inversions probably have value in diagnosing pairs of doubtful zygosity, particularly when blood tests cannot be used. However, the variables of main interest in nature-nurture studies of twins are health status and behavior, and lateral inversions have not been demonstrated to have much significance for those variables.

The mutual circulation

It is equally true that the after-effects of the mutual circulation in monochorial fetuses have not been demonstrated to have significant consequences in the pairs who survive the condition. Since it is unique, or very nearly so, to pairs of monochorial type, its effects would seem peculiarly difficult to distinguish from effects of lateral inversions.

It should be noted, however, that most lateral inversions are directly observable, while effects of the mutual circulation are not. This consideration alone could have occasioned some confusion between these two sources of bias in twin studies. It seems to the writer that the older data on the mutual circulation, together with the later findings of developmental genetics, suggest that effects of the mutual circulation are probably a more important source of bias in twin studies than either lateral inversions or natal factors.

The findings of Schatz and others concerning the mutual circulation are discussed in the next two sections of this review. It is sufficient to note here that the phenomenon affects monochorial twin fetuses from an early stage of gestation until birth. At some stages it may tend, within either fetus, to make the condition of the blood more uniform than it would be otherwise. But even this fact is probably disadvantageous; for normally, from one part of the fetal vascular system to another, there are gradients in the blood with respect to oxygen, hormones, and other factors, and these gradients can only be modified to some extent by the unusual conditions of the circulation in monochorial fetuses. "It is as though one twin continually turned over part of its blood and nutrition to the other" (Schatz, 1887*b*). The more important point is, however, that an even balance in the circulation as between the twins is rarely maintained. Imbalance is apparently the typical condition, due to chance factors of position and growth of placental vessels, as well as torsions in cord veins and arteries which, in the cords of nontwin embryos, are rarely of consequence. As a result, the development of either or both fetuses may be modified at any stage of gestation after the first or second month, and although the surviving twin infants recover from the condition to a large extent, it seems very probable that some of the effects are lasting.

The essential facts concerning the condition have long been reported in medical texts, but in this country Newman (1922, 1923) appears to have been the first to relate those facts directly to studies of mature twins. In *The Physiology of Twinning* (1923) he not only provided a review of Schatz's findings but went on to say:

> ... one cannot help but suspect that, even in one-egg twins that are nearly equal, go to full term, and live for a considerable time after birth, some of the after-effects of minor degrees of the changes listed above may persist in one or both individuals (p. 146).
>
> ... it seems to be quite probable that many of these apparently normal individuals suffer physiologically so as to acquire certain functional heart weaknesses or disorders, and it may well be that the very common difference in vigor or vivacity between one-egg twins is the result of an intrauterine injury of the same kind but of lesser degree than those that are clearly recognized (p. 150).

Among other authors who have discussed the possible after-effects of the mutual circulation are Weitz (1924), Abt (1925), Vignes (1925), Dahlberg (1926), von Verschuer (1927), Lange (1928), Orel (1929), Reichle (1929), J. C. Smith (1929, 1930), Hirsch (1930), Gesell (1931), Rife (1933*b*), Morgan (1934), Lenz (1935), Quigley (1935), D. Jennings (1937), Rosanoff, Handy, and Plesset (1937), Brander (1937*b*), MacArthur (1938), Yerushalmy and Sheerar (1940), and de Siebenthal (1945). The majority of these authors noted that natal factors, lateral inversions, or both, were also sources of bias, but their views as to which kind or kinds of factors might be important in twin studies have

differed strikingly. Moreover, by no means all of these investigators have seemed to believe that the biases were important enough to require substantial allowance for their effects in studies of twins' postnatal status. Apparently as a result, statistical authorities (e.g., Holzinger, 1929; Ignatiev, 1936) have, for the most part, simply disregarded the biases in the statistical schemata they have offered for nature-nurture twin studies.

Another feature of the historical picture has been the fact that several authorities have noted the mutual circulation as a source of bias—and then, in later discussions, have either disregarded the question or given it slight attention, at least as compared with the attention they have given to lateral inversions.

This has not been typical of Newman, for throughout most of his reports and books he has probably done more than any other author to call the attention of his colleagues to all three sources of bias. Nevertheless, or perhaps for that reason, one of his later discussions provides a good example of how interest in lateral inversions seems to have overshadowed questions as to the mutual circulation's effects. As it happened, it was this later discussion by Newman (see Newman and Quisenberry, 1944) that led the present writer to look up much of the material herein, and a few comments on that discussion may help to bring out the need for thorough study of a large number of monochorial and dichorial-MZ cases.

Of the details concerning the very interesting pair which Newman and Quisenberry reported, we need note only the facts that the twins were monochorial (monoamniotic) and concordant in every way except that one infant had an extra thumb. Newman may have been referring to an effect of the mutual circulation in saying that the extra thumb might have been "a somatic modification, a phenocopy, and not hereditary at all." Otherwise, however, the discussion centered on probable effects of lateral inversions acting in combination with the conditions of developmental arrest which caused the twinning. Inviting alternative explanations, Newman remarked that "if we must call upon any sort of environmental differences to account for the peculiar distribution of polydactyly in these twins, those differences must be much more subtle than anything contemplated by geneticists hitherto."

This is not altogether correct, for one might suppose that the genotype of the twins was such that, had they been dichorial, the gene or genes for the extra thumb would have been manifested in both twins to the same extent (which might be to any degree from nil to full expression). Now, the pair was in fact monochorial, and imbalance in the mutual circulation could have occasioned enough of a differential in developmental rates at the "critical" stage to make the expression of the trait different in the two embryos. Presumably this pair's genes were such that the extra digit would have been fully expressed in both twins if no imbalance had occurred (as was the case, incidentally, in the dichorial-MZ pair reported by Danforth, 1919*b*). However, if the gene for the digit and the modifying genes had been such that manifestation of the extra digit would have been slight or nil in a dichorial-MZ pair, imbalance in the mutual circulation could still have caused the difference observed between these twins.

This is not assumed to be a more plausible explanation than Newman's, but seems worth

noting to show that the problem of effects of lateral inversions as compared with effects of the mutual circulation is indeed complex.

Possible studies

With three kinds of biasing factors to be evaluated and information about them available, in the main, from only two types of twins, it is clear that there is no objective way to judge the separate effects of the three biases. Could admittedly subjective, yet reasonably valid, conclusions be drawn if more direct evidence were available as to what happens to twins of the two MZ types during and after birth, and provided this evidence were judged in the light of other knowledge?

The writer believes so. By "other knowledge" is meant indirect evidence, and a part of it is reviewed in the next three sections of this review.

As concerns direct evidence, data on the frequencies of lateral inversions in the two types of MZ twins are needed, and so also is extensive information concerning the natal factors. Of these two problems, the second is much more difficult and expensive to solve than the first, but it is theoretically possible to obtain direct evidence on both.

Danforth's method (1916) of linking observations of mature twins with data on their secundines has already been used to advantage in Europe, and, especially in this country, it could be used to considerable further advantage. One may start with hospitals known to have been collecting reliable information about twins' secundines and "follow up" from the hospital records to such pairs as can be found. Or, one may start with twins in the childhood or young adult age ranges and "follow back" to records of hospitals where they were born or to the records of attending physicians.

It is true that information obtained from physicians not associated with hospitals at the time the twins' births occurred is unreliable, but the percentage of mistaken reports is probably low. If the nature of the information available is published so that the material can be classified according to its probable reliability, even the information obtained from hospitals and physicians not specializing in the subject has considerable value. Something like 2000 dichorial-MZ pairs and many more monochorial pairs have been born in this country annually in the past fifteen years, during which many hospitals and physicians have been collecting fairly reliable information about the twins' secundines. These younger pairs not only yield almost as much information as older pairs, but they are relatively easy to find through school authorities and their parents' cooperation is seldom difficult to obtain.

If one or two hundred "probable" dichorial-MZ pairs and several hundred "probable" monochorial pairs were found by these methods, and if the usual data on lateral inversions, physique, disease history, and school progress were

obtained and published for each pair, the information would help to show what kinds of detailed information are most needed in an intensive study.

The data would be especially useful for indicating how frequently lateral inversions of significant degree occur in dichorial-MZ pairs. Also, some initial judgments might be made about the relative importance of each kind of bias affecting twin studies. The judgments could not be considered convincing, however, if only because they could be affected by selective factors operating in the methods used to discover the cases. Thus, advantageous as it might be to have the data obtainable by these relatively rapid methods, it seems clear that a more intensive study of all three kinds of primary bias affecting twin studies would be desirable.

The cost of an intensive study would be great, due mainly to the difficulties in the way of obtaining adequate and reasonably uniform data on the natal factors. It would nevertheless be important to have such data, because, opinions aside, for all we know now the natal factors may occasion as much bias in twin studies as either of the other two kinds. Despite the long history of discussion concerning the natal factors, the information we have about them today is no more convincing than the information available on them a century or more ago, and the data will remain so until or unless the problem is approached systematically. This does not mean collecting physicians' opinions after twin births have occurred. It means obtaining physicians' cooperation in advance, so that they can start their record-keeping with suspected twin confinements, and thus secure data that are comparable from case to case on crowding, position *in utero*, and all important circumstances of delivery.[1] If the physicians associated with participating hospitals made special effort to do so, it appears that at least 90%, and perhaps 95%, of the twin pregnancies can be diagnosed by about the 32nd week of gestation.

The majority of the cases would, after delivery, be found to be DZ pairs. These cases would not need to be followed very long because all or most of

[1] Norma Ford Walker (see Ford, Brown, and McCreary, 1941) mentioned a study being conducted in collaboration with Toronto hospitals on the fetal circulation in twins, and later (see Walker, 1947) noted that several pairs of dichorial-MZ type were under observation. In correspondence with the reviewer she has advised that the work began in 1937, and now includes data on over 600 twin pairs. Walker has interviewed the mothers at the time of the twins' birth, has injected the fetal circulation in the placenta with liquid latex (of one, two or more colors if necessary), and has carefully ascertained each pair's type of secundines. Several studies of the twins are being conducted by Walker's graduate students and a very interesting report on a dichorial-MZ pair has been submitted for publication. Also, Alan F. Guttmacher has advised that special attention is being given to twin cases in connection with an obstetrical record form which Baltimore hospitals are developing for use in that city. In view of these on-going studies and others that may have been started since the reports of Curtius (1930), Lassen (1931), Steiner (1935), Voûte (1936) and Essen-Möller (1941*a*), it seems worth while to note the desirability of including, wherever possible, identification of twin pregnancies before term and arranging to obtain complete records on the natal factors.

them could soon be excluded by blood tests. However, until these cases could be excluded with certainty by such tests or by other methods, they should be followed in the same manner as the pairs appearing to be definitely dichorial-MZ or monochorial cases.

The form or forms for recording the natal factors should be worked out by obstetricians. It should be possible to make some inferences concerning placentation from the condition of the secundines. It would probably be necessary to arrange, in advance, that only qualified persons would have access to the detailed records of natal factors, as otherwise the chances of obtaining full records would be reduced. Complete information concerning anesthesia and analgesia should be obtained. The reports on the secundines could well be verified by an expert serving as a consultant to each participating hospital.

While the work would need to be done with the collaboration of the local obstetrical groups, the best units for the administrative aspects of the work would be large hospitals. We may consider the number of hospitals and the amount of time required for obtaining the necessary data on natal factors and secundines, assuming that 50 dichorial-MZ pairs are needed and that the birth rate of such pairs is 8 per 10,000 deliveries (cf. p. 300). On the basis of these assumptions, the required number of cases could be expected to occur in a total of 62,500 births.

According to Arestad and McGovern (1949) there were 62 hospitals in the United States in 1948 having large maternity services, i.e. between 3,000 and 10,000 confinements for the year. Only 10 of the 62 hospitals had over 5,000 births each, but hospital authorities have observed that, more or less independently of recent changes in the birth rate, the number of hospitals with large maternity services has been growing steadily in recent years. Since this trend is expected to continue, it seems likely that during the next decade this country will have 15 to 20 hospitals in the group with 5,000 to 10,000 births annually.

If four hospitals, each having between 5,000 and 6,000 births per year, participated in the work over a three-year period, the total number of deliveries should be at least 62,500. As noted above, the requisite 50 dichorial-MZ pairs are to be expected among this number of deliveries. Over 150 monochorial pairs would also be among the same group of deliveries. The number of DZ cases which would occur among the 62,500 deliveries, and upon which comparable records of the confinements and deliveries would have to be kept for a time, would be less than 1000.

These figures serve to indicate the scale of the initial record-taking work that would be necessary for an intensive study. It is clear that the work could be done most advantageously in the larger hospitals, or at least in the larger cities, but administrative arrangements quite different from those assumed above might be found feasible.

As the twins grew up the collaboration of local pediatric groups would be very desirable in order to obtain better cooperation from the twins' parents through furnishing care of the children at nominal cost. The follow-up study of the pairs could well continue for over a decade, but before the end of that

period it should be possible at least to narrow down the existing range of opinions as to the kinds and amounts of primary bias that may be important in nature-nurture twin studies.

As a rationale for judging the results of the study, about all one can say at present is the following. For any one trait or group of traits, we may believe that the average intrapair difference, or average squared difference, observed in the monochorial group will be greater than that observed in the dichorial-MZ group. For brevity this anticipated disparity in the likenesses of the two groups of twins may be termed 'the excess.' The interpretation of the excess would depend on how frequently lateral inversions are actually found in the dichorial-MZ pairs. The various possibilities appear to be:

1) If, as seems most probable, the lateral inversions should be found in the dichorial-MZ group moderately often, but less often than in the monochorial group, then the excess could not be used to estimate the importance of any one kind of bias, and all judging of the relative importance of the three kinds of factors would have to be subjective.

2) If lateral inversions should be found insignificant in the dichorial-MZ pairs, the excess could be attributed to effects of the natal factors alone, since the mutual circulation does not occur in pairs of dichorial-MZ type. That much would be an objective finding, but then the separate effects of the mutual circulation and of lateral inversions in the monochorial pairs would have to be judged subjectively.

3) If lateral inversions should be found about equally often in the dichorial-MZ and monochorial pairs, it would seem reasonable to attribute the excess to effects of the mutual circulation alone. In this event, the separate effects of lateral inversions and natal factors in dichorial-MZ pairs would have to be judged subjectively.

However, long before judgments of the findings of an intensive study come to issue, data collected by Danforth's method may have yielded a better rationale than the above. It seems useful now to discuss some of the indirect evidence available concerning the problem of the mutual circulation's effects.

5. EARLY KNOWLEDGE OF THE MUTUAL CIRCULATION

The abundant twin lore of the ancients appears to contain nothing of importance concerning the common placenta of monochorial cases.[2] However, about A.D. 100 the father of obstetrics, Soranus of Ephesus, recommended the "double ligature" procedure of severing the cord following delivery, i.e., tying off the cord in two places and cutting between them. It is possible that

[2] As Hüter (1845) noted, the treatise *On Superfetation* in the Hippocratic Collection includes a reference to the fact that a twin pair might be born in a single chorion (see Littre, 1853, p. 485). But according to Adams (1849) that treatise is almost certainly one of the several spurious works in the Collection, so the reference to the single chorion proves little concerning the knowledge of monochorial

Soranus, like Portal in 1685, was led to make this recommendation from experience in delivering a pair of monochorial twins. Yet we cannot assume this from the partial text of Soranus' writings that has come down to us (see Lüneberg, 1894). Although the available text shows that Soranus was much concerned with the problems of twin deliveries, he was referring to single deliveries in the passage stating that, in case the placenta's expulsion were delayed, the double ligature should be used. The object, Soranus said, was to conserve the mother's blood.

His recommendation regarding single deliveries was not seriously entertained when, seventeen centuries later, his obstetrics began to be improved upon. But an extended controversy arose as to whether the double ligature was important in twin deliveries. The question was not—nor could it well have been—settled as long as there was doubt about two facts. One was the independence of maternal and fetal circulations, and the other was the existence of monochorial, as distinct from dichorial, twin cases.

The discussion began when the early French obstetrician Paul Portal (1685) declared that the double ligature should always be applied to the cord of the first-born infant during a twin delivery. Otherwise, he said, there would be loss of the unborn twin's blood "from the placenta through the cord . . . and the other infant would be weakened." One of Portal's reasons for the double ligature was, as he said, the fact that twins sometimes had a single placenta. But he also declared that the mother, too, might suffer undue loss of blood through failure to use the procedure. Clearly, he assumed, as did almost everyone else, that the fetal and maternal circulations were in common; and since he did not explain why the double ligature was not essential in single deliveries, its peculiar importance in twin cases was left in doubt. (It is true that before

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cases which Hippocrates and his contemporaries might have possessed. However, of Hippocrates' interest in twins, and indeed his interest from a nature-nurture standpoint, there is small doubt, considering St. Augustine's statement in *The City of God* (book 5) that "Cicero says. . . . Hippocrates has left in writing that he had suspected a certain pair of brothers were twins, from the fact that they both took ill at once, and their disease advanced to its crisis and subsided at the same time in each of them." According to St. Augustine, Hippocrates' statement about the pair was made in opposition to the views of the astrologer Posidonius, who had attributed similarities in twins to their conception under the same stars. Translator Dods (1871) states that Hippocrates' alternative explanation, which clearly implies some understanding of heredity as a factor in disease, is not contained in any extant work of Hippocrates or Cicero, but that it may have been in Cicero's lost work *On Fate*.

Aristotle's factual and fanciful accounts of twins contain nothing on monochorial cases. However, a point of some interest and one which, apparently, is not well known, is the fact that Aristotle offered a statement which is a fair simile for the theory that monochorial twinning is due largely to development arrest. In *The Generation of Animals* (book 4, chapter 4), Aristotle not only observed that double monsters and twins might have a common origin, but added: "If the fetation has been split up, several come to be formed, just as eddies are formed in rivers; here too, if the fluid which is being carried along and is in movement meets with any resistance, two self-contained eddies are formed out of the original one, both of which have the same movement. What happens in the case of fetations is on the same lines."

Portal's book was published the independence of maternal and fetal circulations had been noted by William Harvey and a few others, but the fact was not widely accepted for nearly a century; in 1733, for example, Gibson reviewed the evidence and dismissed the theory as too "remarkable" to be believed.)

Soon after Portal's book appeared, the Dutch authority Stalpart van der Wiel (1687) published his "rare" medical observations. In them Wiel gave credence to some second-hand reports that could only have been erroneous observations of twin placentas. He went on, however, to give a description of a typical monochorial case, stating that the two halves of the placental area "have common communication by means of vessels through which the blood is transmitted." While Wiel's description (p. 331) of a monochorial placenta was imperfect in other respects, it was remarkably accurate considering the time at which he wrote, and was not improved upon for over a century. Although the description offered by Levret (1766) is sometimes cited as the earliest accurate account, it differed in no important respect from the one given by Wiel.

The latter author was also the first to suppose that the common prenatal circulation of monochorial twins accounted for their postnatal similarity "in temperament and other characteristics." This apparently logical deduction was to prove difficult to down, even two centuries later after Claudius and others had shown that quite the opposite conclusion was to be drawn.

During the first half century following publication of the books by Portal and Wiel, their statements concerning monochorial placentas aroused some obstetrical interest, and even more doubt. The attention given to the subject was slight, however, in comparison with the controversy that developed later. The small attention to the question during the early period was not surprising, considering both the slow development of obstetrics and the fact that a monochorial twin birth occurs only once in several hundred deliveries. Dichorial pairs, being relatively frequent, naturally attracted most of the attention of the early authorities.

Apparently no monochorial case occurred even in the extensive practice of the celebrated William Smellie. He was nevertheless the first to try injecting a monochorial placenta, which another practitioner had brought to him; and he was the first to call the attention of his colleagues to the fact that fetal and maternal circulations were independent.

In his *Treatise* (1752) Smellie offered some routine statements on dichorial cases, then added:

> Yet by an instance that lately fell under my observation, it appears that sometimes twins have but one *Placenta* in common: whether or not there were two sets of membranes I could not discover, because they had been tore off by the gentleman who delivered the woman;

but, when the artery on one of the navel strings was injected, the matter flowed out at one of the vessels belonging to the other.

Though Smellie was a friend of the Hunters, he does not seem to have participated in the experiments by which they were able to demonstrate conclusively the independence of maternal and fetal circulations (Hunter, 1774, plates X–XX and XXIV). Yet the fact must have been known to Smellie, for in 1752, well before the Hunters reported the results of their work, Smellie pointed out a simple test of the view that the placenta adheres to the uterus, as he said, "by contact only."

Smellie reasoned that, if it were true that fetal nutrition and respiration occurred by means of circulation of the mother's blood through the placenta, then the maternal surface of the placenta should reveal the supposed openings through which blood passed to and from the uterus, in those cases where an infant and its secundines were delivered in rapid succession. Smellie's test was to place the placenta of such an infant in a basin of warm water before severing the cord. He observed that well before the infant's respiration began, the heart action continued to force blood to the placenta. He pointed out that compression on the arteries of the cord showed that pulsations were taking place, sometimes "with great force." He reported that despite the pressure of the heart action in the cord, "no blood is observed to flow" from the placenta's maternal surface in the basin. In the light of this observation and other considerations, Smellie stated his agreement with unnamed "new theorists" on the point that the fetus is "rather nourished by the absorption of the nutritive fluid into the vessels of the *Placenta* and *Chorion*, than from the red blood circulated in full stream from the arteries of the *Uterus*" (p. 139).

Thus Smellie, by means of the injection, had not only demonstrated beyond all doubt that the mutual circulation existed in monochorial cases, but he had indicated the true obstetrical significance of that fact by pointing out the independence of maternal and fetal circulations. Yet controversy over the necessity of following Portal's recommendation, and indeed over the very existence of monochorial pairs, was carried on for the better part of a century. Then Hüter (1845) finally put an end to the doubts by thoroughly reviewing all the accounts of monochorial cases that had accumulated up to that time. In the course of his review he cited no less than 36 authors' reports on types of placentas and on the question of the double ligature.

To some extent, Hüter also advanced the study of the placental vessels in monochorial cases, using liquids of different colors for injecting the arterial and venous systems of each placental half. It had been generally supposed that the important connections between the two circulations were those observable on the surface of the placenta. Hüter pointed out that these were rarely, if ever, arterial-venous connections, but that arterial-arterial and ve-

nous-venous connections were common. He apparently accepted the idea that the "mutual source of nutrition" through the common circulation of monochorial twins was the reason they often showed "the same primordium for diseases." Yet he observed that some placentas showed peculiar effects of the vascular systems, and remarked that "perhaps the occasional dissimilarity in the twins' development is caused by this repeated and permanent blood stagnation."

Study of acardii

Throughout most of this period of discovery of the more normal aspects of monochorial cases, the question of the origin of acardiac monsters had been attracting attention. Prior to the eighteenth century the literature on acardii had dealt only with a few unusual forms of these fetuses, and their relationship to monochorial twinning and double monsters had been obscured by superstitions.

Scientific studies of acardii began to be reported about 1720, when Mery held that acardii were "more instructive" than double monsters. De Superville (1739) ably supported the view that acardii were not determined at conception, but he felt sure they were caused by the "distorted and disturbed imaginings" of expectant mothers. Others agreed that acardii seemed explained well enough by the widespread doctrine of maternal impression, until W. Cooper (1775) held the doctrine not only wrong but "pregnant with mischief for society." For an alternative explanation of acardii Cooper reverted to the assumption that they were determined at conception. He raised the question as to how the circulation in an acardius was effected, and offered as the answer what he called the "living muscular power of the arteries." Later Monro (1792) and Clarke (1793) were led to offer explanations of the same kind.

Even before the reports of Monro and Clarke, there had been some speculation that the circulation in an acardiac fetus might be maintained by the heart of the normal fetus. No one succeeded in demonstrating the point satisfactorily until Hodgkin and A. Cooper (1836) reported a case in which they were able to show, by careful injections, that the heart of the developed child must have "impelled the blood" through the placenta to the malformed fetus, and indeed, in the reverse of the normal directions through that cotwin. These conclusions were disputed (e.g., by Houston, 1836) until the older views were finally disposed of by Hall (1844).

After H. Meckel (1850) and Schultze (1854), building upon the findings of the early experimental embryologists, had brought out the fact that human monochorial twins must be of uniovular origin, Claudius (1859) published a monograph on acardii indicating several of the key points that Schatz was to demonstrate more thoroughly later on. Claudius held that his predecessors had misunderstood the course of development of acardiac fetuses through fail-

ure to appreciate the exact nature of the vessel relations in the placentas. He extended Hüter's findings and stressed that not enough attention had been given to the capillary system within the placenta, as distinct from the hypercapillary or gross vessels which usually connected the two cords on the fetal surface. Claudius declared that, taken as a whole, the vessel relations of monochorial fetuses comprised "hemodynamic conditions without parallel" elsewhere in the biological world, and he affirmed that the initial development of the heart of the acardius was not necessarily abnormal. He concluded that "the cause of the deformity lies in an accidental position of the placental vessels of the two embryos." Buhl (1861) and Hecker (1864) were among those who confirmed or extended Claudius' findings during the next few years.

Spaeth (1860) disagreed, but his findings were carefully reported and of much value to others. Spaeth collected a large number of twin placentas, including 31 that were monochorial. Since he found the vessel connections present in every case that was sufficiently well preserved to permit careful study, he realized that the mutual circulation existed in all or nearly all cases of monochorial type. And, as it happened, individual fetuses in several of his pairs strikingly showed severe effects of imbalance in that circulation, much as they had already been described by Claudius and others.

Spaeth was well aware of their theory, which he called "the doctrine of a prejudicial influence" of one fetus upon the other. Remarkably enough, he discussed in considerable detail the very cases which confirmed the "doctrine"—and declared that it "obtains no support from these observations." His reasoning was that since one fetus sometimes died without apparent effect on the development of the other fetus, and since this occurred despite the existence of the mutual circulation, it followed, he said, that each cotwin's development must be "independent." He held that "no matter what the condition of the placenta may be, the statement of Crede is correct: 'Each fetus leads a separate existence, independent of the neighboring fetus.' "

Hyrtl (1870) published a folio giving detailed drawings and descriptions of a large series of placentas. Though Schatz, later, was highly critical of Hyrtl for certain errors of interpretation that had arisen from Hyrtl's methods of injecting the placentas, Schatz nevertheless termed the folio "magnificent" (*Prachtwerke*), and said that it, more than any other single work, stimulated him to pursue the subject.

In 1875, a few months before Schatz's initial report was published, there appeared the first of Ahlfeld's *Beiträge* on twins, consisting of four papers which he completed in 1879. In this first paper, Ahlfeld (1875) criticized Claudius' views, holding that in acardii "the circulation of the stronger heart, which means the blood course of the embryo whose allantois was first to develop, overcomes the current in the capillary vessels and thus reaches the body of the second embryo." This represents one of the points which occasioned dis-

putes between Ahlfeld and Schatz. The *Beiträge* also dealt with the causation of hydramnios in monochorial cases, which was the problem that had attracted Schatz's attention. Among other topics discussed by Ahlfeld was the subject of twins' postnatal lives. This discussion, like Galton's report, helped to stimulate research with twins in later years, but Ahlfeld's approach was not concerned with nature-nurture studies in Galton's sense.[3]

Galton's views

As regards Galton's knowledge of the various developments outlined above, the question would warrant a separate review by someone thoroughly familiar with his life and work. It may be noted here that he published his main report on his twin study in four forms (1875*a*, 1876, 1883, and 1907). The last two were in his *Inquiries*, and although Galton changed some parts of that volume for its second edition, he changed the report of his twin study in no important respect. Also, as among the first, second, and third versions, the differences appear to be less important than has been supposed, and none of them are as enlightening on the question of what Galton thought about the types of twins as the two other articles which he prepared shortly after submitting the second version of his main report for publication in the "Miscellanies" of the 1875–76 volume of the Anthropological Institute's *Journal*. (The second version of the main report is here dated 1876 because it apparently appeared in print early during that year, whereas the articles here indicated as 1875*b* and 1875*c* were actually read by Galton at a meeting of the Institute in 1875 and may have appeared in print that year.) His correspondence with Darwin (see Pearson, 1924) merely shows that, as of November of 1875, Galton felt apologetic for having used the expressions "double-yolked eggs" and "simple germs" in his first main report (1875*a*).

The only specific references Galton cited to what he recognized as the "large literature relating to twins" were Spaeth's report (1860) and Kleinwächter's review (1871). From Spaeth's data, Galton derived 24% as one estimate of the proportion of all twin births that were monochorial, and he compared this with "other estimates" which, he said, usually gave 6%. He cited no source for the latter figure, but he may have derived it in some fashion from the data in Kleinwächter's review. For, as Galton said in all versions of his main report, Kleinwächter's book contained misprints; and indeed, there are obvious misprints in that part of the book where data on frequencies of monochorial and dichorial cases are reviewed. These were, apparently, the circumstances which led Galton to make his well known remark (1875*b*) that the statistics on monochorial cases varied "astonishingly."

It should not be supposed, however, that these circumstances particularly affected Galton's assumptions concerning the types of twins His stated objective was to distinguish between the effects of postnatal influences and the effects of "tendencies received at birth." It is possible that he specified "at birth" because he had read of possible effects of the mutual circulation in Kleinwächter's book, where the history of that question, beginning with Smellie's injection, was reviewed. But this possibility appears remote, because Galton also spoke of qualities "inherited at birth," and he nowhere cautioned his readers to distinguish between birth and any earlier period of gestation. Moreover, as will be evident from the statements quoted below, Galton had his own theory for what he supposed were extreme MZ differences. This theory was so inclusive that, even assuming Galton had read all of

[3] Ahlfeld's other major paper on twins (1902) represents one of the historically unfortunate efforts to explain away Weinberg's confirmation, in 1901, that the excess of same-sexed twins was too great to be accounted for solely in terms of the frequency of monochorial pairs.

Kleinwächter's book, he would hardly have felt there was need to consider findings like those of Claudius.

He believed 20 of the same-sex pairs which he had studied were "strongly dissimilar" MZ cases. It is clear—today—that all or most of them must have been DZ pairs. Galton had not studied them at first hand, and the findings from his questionnaires concerning them (which he abstracted in his 1883 report) reveal nothing but statements of the kind which parents and friends typically make concerning DZ pairs. Galton was fully aware of the fact that half of all DZ pairs were of the same sex (1875*b*). Yet, even so, he had somehow become convinced that all or most "strong dissimilar" same-sex pairs were MZ cases.

He so indicated in several places, most explicitly in his article on *A Theory of Heredity* (1875*c*). There he said he considered his 20 very dissimilar same-sex pairs to be "true twins," and he went on to define true twins as "those who, up to the time of their birth, were enclosed in the same membrane, and had therefore been developed out of two germinal spots in the same ovum." Among all pairs of that type he believed "there exist two groups of cases which contrast strangely with one another. . . . In the larger of the two groups, the twins are exceedingly alike in body and mind. . . . In the smaller group, which contains perhaps one fourth as many cases as the larger group, the twins are absolutely unlike." He accounted for the larger group in the usual terms. To account for the smaller group he said "we might expect that if there had been a sufficient delay before the division . . . the twin halves of the primary stirp would be strongly contrasted."

It is hardly surprising that Galton held this theory, for numerous other authors before, during, and after his time were led to offer explanations of MZ differences more or less like Galton's. It is, however, unfortunate that Galton did not continue his study of twins. For he would surely have seen that MZ pairs did not, as he had supposed, fall into two clear-cut groups in respect to intrapair differences. He would not only have seen that his 20 "strongly dissimilar" pairs were DZ, but, during the next two or three decades, he might also have found substantial evidence for his insightful statement concerning similar pairs that "it is not necessary to ascribe the divergence of development, when it occurs, to the effect of different nurtures, but it is quite possible that it may be due to the late appearance of qualities inherited at birth." (Galton's findings on these and other initially similar pairs are reviewed in section 8.)

His intention to pursue the question was clear from a sentence in his first report (1875*a*). He said: "On this curious point, and on much else in the history of twins, I have many remarks to make, but this is not the place to make them." He was referring to his theory that extreme dissimilarity was largely or entirely peculiar to MZ pairs. Shortly afterward (1875*c*) he offered his explanation in terms of "delay before the division." He was probably not satisfied with that account. For in each of the three later editions of his main report (1876, 1883, and 1907) he left unchanged the sentence indicating that he would have more to say on the problem. No such further account of his views has been found by the present writer.

6. SCHATZ'S FINDINGS

As compared with the several other reviews of Schatz's findings (1875–1910*a*) which are available,[4] this review attempts to give more attention to

[4] In addition to Newman's review (1923), comprehensive accounts of Schatz's findings have been given by Strassmann (1904), Hübner (1912), and Weber (1924), while Englehorn (1927) afforded a brief account. Ahlfeld, though stressing his own views rather than those of Schatz, covered the subject in his text (1900 and 1903). The English translation of Winckel's first edition (1890) contained a summary of Schatz's early work, as have also most revisions of Browne's text (1946). Pertinent

points that may bear on questions of the mutual circulation's effects on twins' postnatal status. These are, in general, the less severe effects, inasmuch as only less affected pairs survive birth and infancy.

Unfortunately, Schatz had relatively little interest in the less severe effects. He was an obstetrician rather than a pediatrician, and he was preoccupied with the subject of embryonic and fetal development. He was interested in noting which pairs survived birth and the first few weeks thereafter. But, if he had views concerning lasting effects of the mutual circulation in the surviving pairs, he left those views to be inferred from his work as a whole.

In any event, for purposes of the next section of this paper it seems essential to review the main features of Schatz's work in some detail. However, it wolud not seem necessary to deal with the technical disagreements between Schatz and others over the problem of hydramnios in monochorial pairs, nor to consider the merits of the disputants' views as to how often acardiac conditions originate before and after the second month of embryonic life. Omitted also are Schatz's detailed inferences concerning relatively "favored" and "disadvantaged" cotwins at different stages of gestation, except for noting here his view that the twin who was smaller at birth often had somewhat better chances of recovering from the mutual circulation's effects than the larger infant. This would seem to mean, for example, that one should not expect to find a very marked relationship, within pairs, between birth weight and adult status.

Schatz changed his basic views little, and his first and second papers appear to justify his remark later (1910*a*) that the "whole plan" of his work on monochorial twins had developed in his mind by 1875. But he extended and supplemented his views a good deal as he went along, and there are some apparent, if not real, inconsistencies in the work as a whole. Most of them involve terminology and are probably minor. Since Schatz does not seem to have reconciled all of them, it is here assumed that he intended his later views to stand as his considered ones.[5]

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though brief, statements concerning the subject have been carried in most editions of Williams' text (1941).

Schwalbe's *Handbuch* (1907) contained a discussion of Schatz's findings which, though sometimes cited as authoritative, was based largely on a review by Marchand (1897) that was far less adequate than, for example, the later review by Strassmann. Also, some confusion concerning the general subject appears to have arisen from Ballantyne's popular *Manual* (1905). It dealt with the studies of Claudius, Ahlfeld, and Schatz, but without distinguishing very clearly between their findings and Ballantyne's own view that, while deformities in nontwins were largely due to such environmental factors as alcoholism and other "noxa," heredity was the chief cause of differences between monochorial twins.

[5] All except the first and last of his reports were re-published as a volume (1900*a*) on "The physiology of the fetus," a title which reflected Schatz's belief that his findings contributed to the science of developmental mechanics that had been growing rapidly under the leadership of Roux (1888). As part of this volume, Schatz prepared a detailed table of contents and indexes of all authors and subjects discussed in the 685-page series of reports. The volume is evidently in few libraries in

Techniques and main findings

Schatz's usual method of studying monochorial placentas was to inject thin liquids of four different colors into the cords, so that two of the colors brought out the arterial and venous systems in the placental half of one twin, while the other two colors showed the arterial and venous systems in the co-twin's placental half. Before injecting, he prepared a sketch of the placenta. With this at hand he observed the course of each injection while its flow was taking place, filling in this course on the diagram as rapidly as it was revealed. He "controlled" the injections by limiting the amounts of fluids used and by compressing the placenta in such a way as to prevent too rapid diffusion through the vessels.

He confirmed his predecessors' findings that the more obvious class of connecting vessels, or the hypercapillary ones running irregularly between the two cords on the surface of the placenta, were always of the same kind; that is, they were either connections between an arterial vessel of one placental half and an arterial vessel of the other placental half, or between a venous vessel of one half and a venous vessel of the other half.

He further confirmed that the capillary or villous connections within the placental parenchyma were always of opposite kinds, i.e., either arterial-venous or venous-arterial connections between the two placental halves. Schatz saw that in these capillary vessels "the exchange of blood takes place with great energy . . . due to the difference in pressure between the arterial and venous blood." He believed that estimates of the blood volume passing connections of this class could be made from "the calibre of the vessels leading in and out" of the particular area where villous branches made contact between the placental halves. He thus deduced that the total volume passing these connections in one direction sometimes differed from that passing in the other. From this fact (together with various effects observed in the fetuses) he inferred that the relatively slow movement of the blood through the hypercapillary connections on the surface of the placenta did not always compensate completely for the difference in the volumes passing through the capillaries.

this country, but its table of contents and indexes were also published separately in the *Archiv*. Together with his "Addendum" (1910*a*), Schatz's table of contents and indexes (1900*b*) provide excellent guides to his findings and views.

We may also note that his more important publications on subjects other than twins were brought together in a volume entitled "The physiology of pregnancy" (1910*b*), which includes a remarkably extensive collection of data concerning duration of pregnancy. In the course of his career at the University of Rostock, Schatz founded an outstanding maternity clinic and organized a school for midwives which was credited with greatly reducing maternal mortality throughout Mecklenburg province. Students and midwives respected him, but felt that he was unduly exacting. "Perfectly as he mastered a subject for himself, little was he a master in the reproduction of his ideas" (Büttner, 1920; see also the notices by Oldag and Prochownik of the same date, the year of Schatz's death). These and other features of his character, added to the inherent complexity of the problems which he undertook to solve, may account in some part for the slowness with which his findings have been accepted.

He saw that what some authorities had thought was direct mixing of the twins' blood *in the placenta* was scarcely possible in view of the "anatomical arrangement" of the vessels. Yet this very arrangement typically meant, he said, that some 5 to 20 per cent of the blood was directed more or less continuously from the heart of one twin into the vascular system of the other. And since compensation through the hypercapillary vessels was frequently incomplete, the mutual circulation was "dynamically asymmetric" or imbalanced over substantial periods of time, with resulting differences in the twins' development during those periods. Schatz stressed that the degree of "asymmetry" of the mutual circulation did not depend upon apparent asymmetries in the physical structure of the placental vessels, but upon whether "the same amount of blood flows in one direction as in the other during a given period of time," whatever the combination of vessel structures involved.

With regard to frequencies of the two classes of vessel connections, Schatz found that the villous or capillary connections varied markedly from one case to another, but that at least a few were present in every one of "about 100" monochorial placentas which he was able to examine over the 35-year period.

With respect to frequencies of the gross or hypercapillary connections, for which he reserved the word "anastomoses,"[6] his reports indicated that 8 of the 100 placentas showed neither an arterial nor a venous connection; about 60 showed only an arterial connection; only 2 showed a single venous connection; and about 30 showed both an arterial and a somewhat smaller venous connection.

These frequencies should not be considered as exact, however. They are cited here only to give some idea of the variation which Schatz encountered in the "placenta types," as he termed them. The figures were estimated by the present writer, considering certain numbers and percentages which Schatz mentioned in two of his later papers (1898, 1910*a*). Doubtless because Schatz knew his samples were small and possibly biased, he was cautious concerning the proportions of these types.

He was even more cautious concerning specific effects that were to be expected in connection with them. For cases having any one of the four placenta types, he said, the mutual circulation might sometimes develop in a more or less balanced fashion and remain so throughout fetal life, so that no significant effects occurred except for slightly enlarged hearts in individual fetuses. At the same time, he stressed that any one of the four placenta types could be associated with "the most varied consequences" in the twins. Nevertheless, he

[6] This usage is followed here for convenience. Schatz's substitution of the term "third circulation" for the older name "mutual circulation" is not followed, however. Schatz intended his term to connote the biological uniqueness of a circulation involving two hearts; but, for that purpose, his name for the phenomenon appears to have been no more effective than the older one.

offered a few generalizations concerning the separate types that seem worth noting.

Twins of the infrequent type whose placentas showed no anastomosis seemed most often to suffer severe effects of imbalance in the mutual circulation, as was to be expected, he said, in the absence of compensatory anastomoses.

Twins of the most frequent type, or those with an arterial anastomosis, appeared to have fairly good chances of surviving to birth and thence overcoming any effects which the mutual circulation might have occasioned prenatally. It is of incidental interest that a twin pair of this type was the only pair which Schatz followed up for any length of time. He found that during the first seven weeks of postnatal life the smaller twin, whom he considered somewhat "moisture deficient" at birth, gained proportionately more than the larger twin, who had appeared slightly edematous at birth.

Twins of the rare type with only a venous anastomosis were sometimes discussed by Schatz in connection with those just mentioned, and again he grouped them with the type discussed below; we may believe that he did not consider his information (two cases) about this type sufficient for separate generalization.

He believed that the type having both an arterial and a venous anastomosis probably permitted the highest proportion of cases to go to term without serious effects. Yet cases of this type, according to Schatz, were also the most vulnerable to the development of acardiac conditions. When twisting or any other type of stricture in one twin's cord blocked the venous (oxygenated) current from that twin's placental half to its heart, the blocked blood was sent to the cotwin. While the one twin thus lacked a normal supply of oxygenated blood, the other twin not only received too much, but its heart tended to equalize the pressure by sending arterial (vitiated) blood into the first twin through the arterial anastomosis. If this condition were not relieved, normal vascular functioning was drastically altered in the twin with the constricted cord. Its heart action was weakened, and subsequently might be stopped altogether. In the latter event its circulation was maintained only by the heart action of the other fetus, with the normal directions of the blood streams reversed in the acardius. A few such cases were traceable to conditions arising even before the definitive cord was formed, Schatz admitted, but he held that the principle was similar in that restrictions of the "venous inflow" were the initial causes of the deformities.

To Schatz, these four types of placentas had the merits that they could be studied objectively and afforded certain clues, but he did not regard them as the basic desiderata. In fact, he appears to have placed decreasing emphasis on them after giving particular attention to them in the earlier reports. The more important variables involved in the mutual circulation were, he found, the extent of its volume and the degree of its "asymmetry." He found these two variables largely independent throughout his sample.

As already indicated, he believed the volume variable could be measured with considerable accuracy by summing up the calibres of those vessels which led directly to the "transfusion areas" between the two placental halves, the anastomoses being relatively unimportant so far as total volume was concerned.

By the asymmetry variable Schatz of course meant the extent of the mutual circulation's imbalance as between the two twins. Since effects of this variable were not accountable in terms of structural asymmetry of the vessels, he said

it was to be inferred from the effects which it, in combination with the volume variable, had occasioned in the cotwins. In so stating, he added that he knew his logic was open to criticism for "moving in a circle" or begging the question. But he held that the circle could be broken by noting "consistent" relationships discoverable through intensive study of large numbers of cases. Systematic efforts of this kind comprised, in fact, the essence of Schatz's method and contribution. While recognizing the gaps in his own data, he called repeatedly for further collaborative efforts among obstetricians to fill these gaps with sufficient numbers and kinds of cases.

In addition to the mutual circulation's volume and asymmetry, certain secondary variables were taken into account in one or another of the theoretical schemes which Schatz offered from time to time. Of the secondary variables the most important one was the factor of "torsions" and other constrictions occurring in the cords of the twins. Some of Schatz's inferences concerning effects of this variable are covered in the accompanying plates, which are reproduced from one of his later reports (1887*b*). The original plates were in three colors. Without the colors, and with the inaccuracy necessarily involved in photographing such detailed sketches, the plates as shown herein can serve only to suggest to the reader the remarkable presentation of Schatz's views that is to be found by consulting the drawings as he originally published them (preceding p. 335, vol. 30 of the *Archiv*).

In figures 1–6 of these sketches Schatz indicated effects of two degrees of the volume variable (small and large) in combination with three degrees of the asymmetry variable (none, moderate, and marked). Although he believed that the effects of marked asymmetry tended to be somewhat greater when the volume was also large, he observed that this relationship was complex and subject to various qualifications which he detailed.

In figures 7–12 he represented effects of cord torsion in combination with each of the four types of placentas. Figures 13–18 brought out other combinations of conditions which, up to 1887, Schatz had seen reason to believe were important.

He offered accounts of the interactions of all these variables, and of their effects on the relatively "favored" and the relatively "disadvantaged" cotwin fetuses. He extended his earlier views (1875) on the sequence of physiological events which, as a result of imbalance in the mutual circulation, gave rise to the well known conditions of hydramnios and oligamnios associated with respective monochorial fetuses. These views need not concern us except for noting that the contingent moisture differences have an obvious bearing on the discussion of physiological genetics in the next section of this paper.

Early embryonic development

Schatz believed that a complete understanding of the mutual circulation could be achieved only by discovering how the two different classes of vessel

connections between the placental halves came about in embryonic development, and he therefore gave much attention to this problem. He made considerable use of the data being accumulated in the new field of comparative embryology, combining what was known about early development in mammalian twin and nontwin embryos with his own inferences from human cases.

The present writer cannot judge whether Schatz's descriptions of early vascularization conform closely to modern understanding and terminology concerning this process. The two layers of what is now called the "magma reticulare" may or may not have been those to which Schatz traced the origin of the two classes of vessels connecting the placental halves of monochorial cases. But Schatz's description of the amorphous nature of the early vessels and their development or atrophy in accordance with their functioning or nonfunctioning would seem plausible enough in the light of the description of this process in nontwin development given by Hamilton, Boyd, and Mossman (1945).[7]

Schatz said (1910*a*) atrophy of the non-placental portions of the "primary chorionic vessel network" normally began during the sixth week, and was usually complete by the time the definitive placenta developed in the third month. During the first two months the mutual circulation, as such, had "no untoward effects because the anastomoses equalize any possible development of dynamic asymmetry." With the development of the placenta, however, obliteration occurred for all anastomoses except those left functioning to compensate any inequality that had developed in the transfusion currents between the two twins. The transfusion currents developed equally up to this stage in a small proportion of the cases. He inferred that in these cases, owing to the equality, all surface anastomoses between the placental halves atrophied and gave rise to the type already noted as comprising about 8% of Schatz's placentas. During the later stages of these and most other cases, Schatz believed that as the transfusing villi continued to develop in the growing placenta, their development was rarely equal. Since little or no further growth of anastomoses was possible, they could not, thereafter, "accommodate the needs for

[7] According to these authors (pp. 36–38 and 129) the magma reticulare normally develops in the primary mesoderm during the second week, and then separates into two layers. One layer develops with the trophoblast, forming a part of the chorion and vascularizing it. The other layer develops with the amnion, vascularizing it and the yolk sac wall. Thus, at the beginning of the third week, when the embryo can no longer derive nutrition by diffusion, these mesodermal layers develop rudimentary vessels and a simple circulatory system is formed in the embryo, chorion, yolk sac, and connecting stalk. Nourishment of the embryo proper is achieved by vessel rudiments extending to the arterio-capillary-venous systems, which concurrently develop in the chorionic villi. The earliest true vessels in the embryo's body are simple endothelial tubes in which arteries and veins are not structurally distinguishable. They form a diffuse plexus from which "separate plexuses are elaborated . . by fusion and confluence of adjacent ones, while portions from which the flow has been diverted undergo regression and atrophy." Though the process is not completely understood as yet, it is believed that the final pattern is affected by the direction of flow and pressure of the blood.

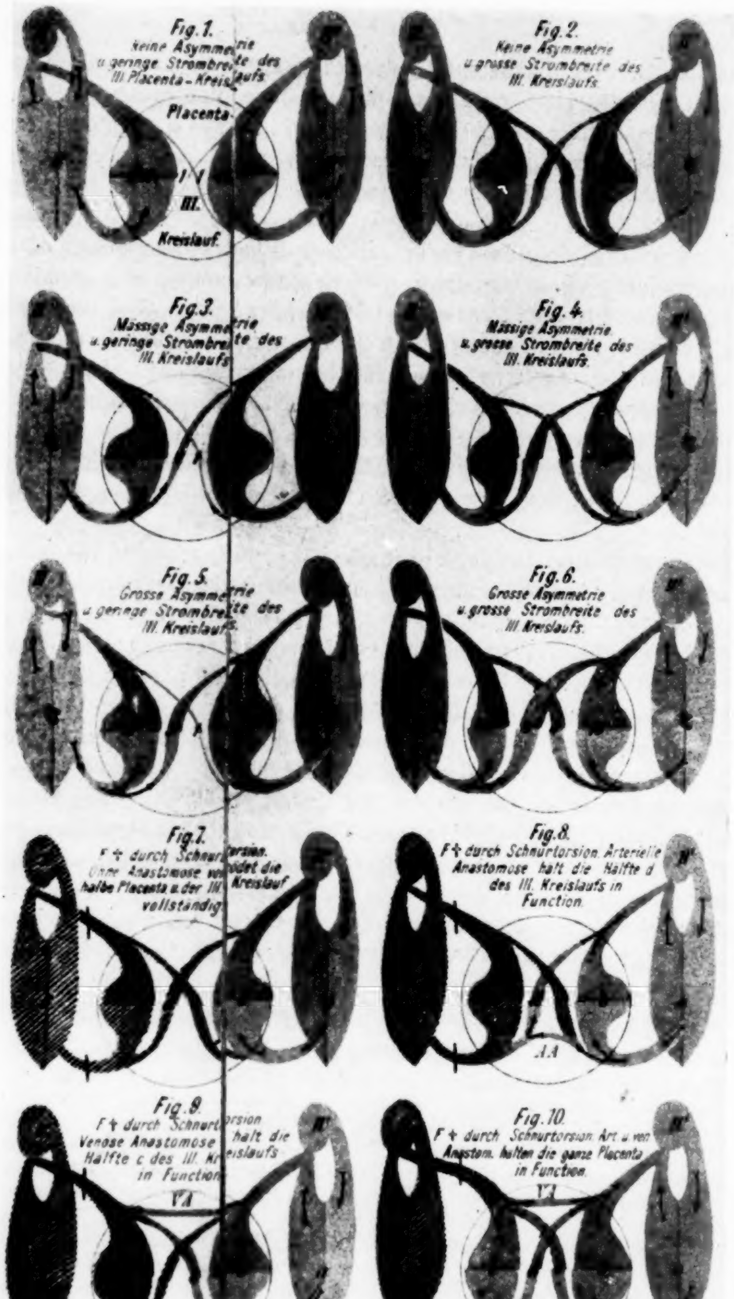
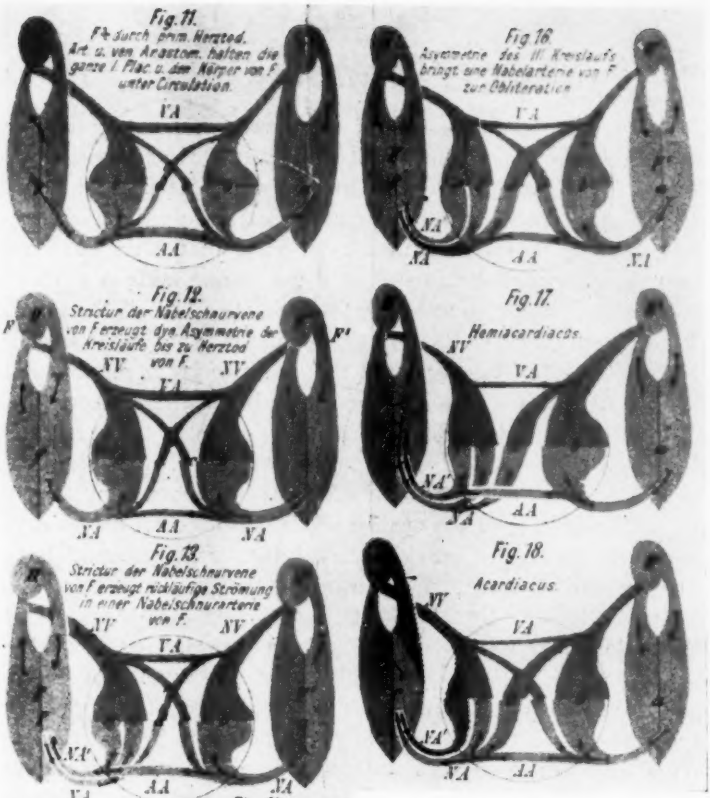


Fig. 1.
Keine Asymme rie
u. geringe Strombre te des
III. Placenta-Kreis aufs
Placenta
III.
Kreislauf.
Fig. 2.
Keine Asymmetrie
u. grosse Strombreite des
III. Kreislaufs.
Fig. 3.
Mässige Asymme rie
u. geringe Strombre te des
III. Kreislaufs
Fig. 4.
Mässige Asymmetrie
u. grosse Strombreite des
III. Kreislaufs.
Fig. 5.
Grosse Asymme rie
u. geringe Strombre te des
III. Kreislauf
Fig. 6.
Grosse Asymmetrie
u. grosse Strombreite des
III. Kreislaufs.
Fig. 7.
F † durch Schnur orsion.
Ohne Anastomose ve ödet die
halbe Placenta u. der III. Kreislauf
vollständig
Fig. 8.
F † durch Schnurtorsion. Arterielle
Anastomose hält die Hälfte d
des III. Kreislaufs in
Function.
AA
Fig. 9.
F † durch Schnurt orsion
Venose Anastomose hält die
Hälfte c des III. Kr eislaufs
in Function
VA
Fig. 10.
F † durch Schnurtorsion. Art. u. ven.
Anastom. halten die ganze Placenta
in Function.
VA
AA



FIGS. 1–18. Variations in the mutual circulation in monochorial twins. [After Schatz (1887*b*) in *Archiv für Gynäkologie*, Berl.]

In addition to the captions shown in these figures, Schatz noted in the text (pp. 171–172): "In figures 1–6, the anastomoses are not shown as separate parts of the third [mutual] circulation, but are reckoned into the total volume of the transfusion currents, since it is known that in any given case they simply convey blood in one direction. In figures 7–18, the anastomoses are sketched separately (*AA* = arterial anastomosis and *VA* = venous anastomosis) because there they involve special functions. The designations are the same throughout, and where it has not been feasible to sketch them all in, they may be completed from the other figures."

compensation," with the result that imbalance in the mutual circulation was a frequent condition.

As to why the transfusing villi of the cotwins did not develop equally, Schatz said the two sets of villi did not have quite the same "positions . . . nor equally good nutrient media on the uterine wall." He noted that with the evolution of upright stance in the primates, maternal nutrition of the embryo had been insured through concurrent evolution of the decidua capsularis. But then the embryo, being carried with the uterine walls in a more or less vertical position, "could no longer lie freely in the uterus." Thus one should note, he said, that evolution had left the primates with ill-suited "arrangements with respect to the median plane" of the uterus so far as monochorial twins were concerned. Since Schatz had found that in most monochorial cases the two placental halves had developed more or less obliquely to the median plane, he believed differences in the growth in the two sets of transfusing villi were understandable as a "consequence of differentially favorable nutrient media" in those portions of the uterus against which the placental halves developed. As to why evolution had not provided the requisite "arrangements," he declared that "nature had no intention of furthering the development of twins" in humans.

These evolutionary views appeared mainly in his last paper (1910*a*), and apparently he undertook to discuss this aspect in some detail because an unnamed critic had, he said, called his views "contrary to the purposiveness of nature's way." His more important point seemed to be that the factors of position on the uterine wall, with consequent differentials in placental nutrition and growth, did not usually cause important differences in the twins' development until about the third month. Then, although gross features of the placental halves gradually became fixed, differential growth of the transfusing villi continued. This usually caused imbalance of the mutual circulation, he repeated, because compensatory growth of anastomoses ceased to be adequate or was not possible at all.

Lateral inversions

Schatz evidently regarded this phenomenon (including all degrees of *situs inversus viscerum* and structural asymmetry reversals in the cotwins' bodies) as a real but not necessarily an important factor in the development of monochorial cases. He discussed this topic (1887*a*) when he attacked the view of Spaeth, who, as we have seen, believed that monochorial fetuses affected each other no more than dichorial fetuses. Schatz said this view must be wrong, if for no other reason than the fact that partial transverse situs occurred relatively often in monochorial cases. He remarked that "insofar as the vascular system enters the picture, partial transverse situs may be injurious or fatal."

He noted that there was a relationship between the occurrence of transverse situs on the one hand, and on the other the embryos' nearness to each other or incompleteness of separation. He said a certain epignathous case (a small malformed twin joined orally with the cotwin) suggested that at the time of *anlage* of the hearts the epignathous cotwin may have had "enough influence, due to restricted space, to produce partial transverse situs in the twin who later developed completely." Though Schatz regarded partial transverse situs as a difference-producing factor of real consequence, he said cases involving it were "rare and easily recognizable."

Later (1900, p. 204) he said "transverse situs, if quite complete, will scarcely lead to restriction of the current in the cord vein; but when transverse situs is imperfect, it will occasion more such restriction." At the same time he stressed that most acardii develop from normal embryos and that "only a small proportion show transverse situs; in respect to this characteristic the large majority of acardii must have been primarily normal." Finally, he apparently included cardiac reversals among "primary" heart defects when he offered his last generalization (1910*a*) on the causes of acardii:

> It is true that acardii sometimes develop through primary defect of the heart, but it is incorrect that most cases develop in that manner. The great majority arise only secondarily, through the vessel communications between the cotwins. Some cases may develop even during the period of the mutual yolk circulation, and acormi cases may arise through involvement of the yolk vein. But most acardii develop only through the allantoic or placental circulation. Indeed, any acardius having a cord can only have developed in this manner, as also do quite a number of the cases involving umbilical hernia.

Developmental mechanics

The above covers important features of Schatz's views in broad outline. There remain to be noted a few points in his work that seem of special interest from the viewpoint of developmental mechanics. In the first place it seems possible that Schatz may have underestimated the significance of imbalanced conditions in the mutual circulation which, he said, were typical of the second month of embryonic growth, or during the period when anastomoses could easily develop to compensate the imbalances. He believed that differences in the blood pressures of the developing embryos were common, and that these differences probably changed often in direction as well as amount during the second month. But he drew a distinction between pressure differences and volume differences, and believed that so long as anastomoses could develop to relieve any significant volume differences, the pressure differences were not important (1898). Considering modern understanding of embryonic growth processes, as noted in the next section of this review, one must wonder whether Schatz was correct in assuming that effects of imbalance were not important before about the eighth week of development.

In any event, Schatz was certain that disturbances in the mutual circulation were frequent after the second month of monochorial twins' growth, and he stressed that a number of different factors occasioned such disturbances. As to their effects on the fetuses, he believed the following consequences were typical when the mutual circulation's volume was small:

> Temporary disturbances in blood distribution and in blood pressure arising in either twin from movements, cord pressure, etc., can be compensated only very slowly once they have occurred. Since these disturbances are frequent, and since they have after-effects of long duration as a result of the slow compensation, they are not without permanent effects. Such disturbances extend to both twins, because they may now affect one fetus and, at a different time, the other.

In the same report (1887*b*) he discussed what he called "chemical" effects in connection with cases where the mutual circulation's volume was large, and offered a comment which seems in line with modern views of hormonal reactions in embryonic growth:

> Through this rapid and complete mixing of the twins' blood, just as soon as one fetus produces blood changes, there is a loss of normal self-regulation. That is, there occurs some reduction in the reaction which otherwise takes place in one organ's activity through blood changed by some other organ's activity. Organic maladies occur quite readily, of course, as a result of this disturbance to the self-regulation of the organism.

In this connection he devoted a "Special section" to tables and discussions concerning actual measurements he had taken of the hearts, livers, kidneys, and other organs of fatally affected monochorial fetuses (1887*b*, pp. 378–381). Later, believing that blood samples which he took from certain twin fetuses would show differences with respect to hemoglobin, he obtained confirmation of such differences from Westphalen (1897).

7. SIGNIFICANCE OF SCHATZ'S WORK

Although the evidence is indirect in nature, there is much support for the inference which Newman drew in 1923 as to possible effects of the mutual circulation in pairs who survive birth and infancy. We need cite this indirect evidence only briefly. It derives from the findings of experimental embryology and physiological genetics, and many reviews of the data in these fields are available, e.g., those by Huxley and de Beer (1934), Morgan (1934), Spemann (1938), Weiss (1939), Waddington (1939, 1940), Landauer (1941), Grüneberg (1947), Gruenwald (1947), and Moore (1947).

Westphalen's verification of hemoglobin differences in certain monochorial fetuses, together with the frequent condition of hydramnios-oligamnios in such pairs, remind us at once of Stockard's observation (1921*b*) that variations in oxygen supply and moisture are two of the three most frequent causes of abnormal development (the third being temperature). Stockard found that when

one or another retarding agent was used to slow embryonic growth at a critical stage, and then removed in time to permit growth to continue more or less normally, various parts of the mature animal's organs were "suppressed, poorly expressed, or deformed." Riddle (1923) went on to show that deviations in development produced by accelerating factors (e.g., excess supply of oxygen) could be as large, if not as frequent, as deviations caused by retarding agents, and that a period not critical for a retarding agent might be critical for an accelerating one.

Waddington (1932) found that the action of "organizers" is by no means limited to the earliest embryonic stages. His data were consistent with Stockard's findings as to critical stages, in that, typically, an organizer was effective for a limited period only, during which the cells were "competent" to react to the organizer's influence. The latter influence appeared to be exerted, as often as not, through the action of morphogenetic hormones. Observations of this kind have been extended in numerous researches, until Parpart (1946, summarizing discussions by H. M. Evans and J. S. Nicholas on hormones as "regulators" of embryonic growth) was able to report:

> Thus the synthetic processes required in growing cells are called forth by hormones [which] act by controlling the rate of enzyme reactions or by changing the orientation of the reactions. . . . An important aspect is that all of the synthetic reactions proceeding under the control of enzymes must be doing so at the peak of efficiency.

Consistent with the findings of experimental embryology are the data of physiological genetics. Goldschmidt (1920 and 1927) stressed that genes often act by increasing or decreasing the reaction rates of metabolic processes at certain stages of development, and he noted the close similarity, if not identity, of the effects of certain genes and environmental agents. He introduced (1935) the term "phenocopies" for characters which, though induced by environmental agents and not heritable, cannot be distinguished in the individual from genetic characters except by breeding tests. He later held (1940) that the phenocopy of "any possible mutant gene" could be produced experimentally, provided certain conditions of the gene's action were known and "an experimental agency is available which produces the necessary shift in velocity" at the critical time.

Among numerous experimental studies of this question have been those conducted by Danforth (1932) and by Landauer and his associates. In a recent report (Landauer, 1947) the findings are reviewed, and it is concluded that several of the abnormalities induced by environmental agents were "true phenocopies."

It happens relatively often, of course, that the resemblance between effects of environmental agents and genic action is only moderately close. When that is so—or when some difference between the two resulting phenotypes

can be established—the effect of the environmental agency should be termed a "non-heritable variation," in order to preserve the meaning which Goldschmidt assigned to "phenocopy." Useful and important though this distinction is for theory, it should be noted that among humans, for whom breeding tests are scarcely feasible, "non-heritable variations" and true phenocopies are all too easily confused. It seems admissible to use the expression "phenocopic effect" for human variations where the difference between true and near phenocopies is difficult to diagnose.

Wright (1945), while not accepting all of Goldschmidt's views, has commented that although the genes are the "ultimate internal" agents, they can act only by "determining one or another reaction of the cells to local conditions." Indicative also of the convergence between the findings on embryonic growth and the data of physiological genetics are the views (1947) of Muller:

> It has long been suspected that the genes act directly as enzymes, each thus controlling a definite reaction or group of reactions, or else that the primary gene products are these enzymes. . . . Just as a given gene will give what we regard as its characteristic effect only in a certain region of the body and at a certain stage of development, so too it may require for such expression a certain environmental condition, or conditions within a certain range—it otherwise may give effects that are different in degree or kind.

Since hormonal and enzyme controls are exercised largely or entirely through the circulation of the blood, and since the conditions of the mutual circulation in monochorial twin embryos are more or less abnormal so far as the distribution of the blood throughout the vascular systems is concerned, the significance for monochorial twins of the various findings and views cited above requires little comment.

Vasculogenesis of the human embryo begins during the third week (Hamilton, Boyd, and Mossman, 1945). As we have seen, Schatz did not think that the mutual circulation of monochorial twin embryos affected their development until about the eighth week; he recognized that imbalanced vascular relations tended to be quite as frequent a month before that time as afterward, but he assumed the condition was not important so long as hypercapillary vessels could develop to offset the imbalances. Now if, as Parpart and others have stressed, normal development requires full efficiency of the hormonal and enzyme controls, we may doubt Schatz's assumption and believe that imbalanced vascular conditions could begin to affect monochorial twins' growth at about the fourth week of embryonic life. Indeed, one need not assume, necessarily, that an imbalanced condition would have to arise for there to be some degree of effect, for even a balanced diversion of a considerable part of each embryo's blood from its normal course and functioning might cause some lowering of the general efficiency of the controls in both fetuses.

The last point may be open to some doubt, but it would seem reasonable

to believe that, beginning at about the fourth week, *imbalance* in the mutual circulation may alter the reaction rates involved in the growth of either twin at any time until birth. Following birth, as Schatz and other obstetricians have noted, there is considerable recovery from the effects of imbalance in those pairs who survive the hazards of the neonatal period. Yet, as we have seen from the findings of experimental embryology and physiological genetics, there is reason to expect that some of the effects are lasting.

We can thus account plausibly for many kinds of differences actually observed in the postnatal status of monochorial twin pairs. For example, one twin may be handicapped in several ways as compared to his cotwin. That is, there may be intrapair differences in respect to several variables, and with all such differences more or less unfavorable to one of the two individuals. With respect to such a pair it seems likely that, prenatally, there was imbalance of the mutual circulation in one direction most of the time. On the other hand, it is well known also that an occasional pair show differences that are quite specific to the two individuals, so that among the variables studied there is little consistency in the direction of the differences within the pair. It seems clear that such differences could arise from changes in the direction of imbalance in the mutual circulation at different stages of embryonic or fetal life.

It seems apparent also that after-effects of imbalance in the mutual circulation might occasion differences in monochorial twins' ages of disease onset, or in their susceptibilities to disease. As regards sensory functions, moreover, there appears to be no reason for assuming that whatever embryonic stages may be "critical" in the growth of sensory structures are limited to the first four weeks. In fact, such knowledge of early human embryology as we possess (see collections of data reviewed by Hamilton, Boyd, and Mossman) suggests that many of the critical stages for sensory structures are in the second or third month, so disturbances in the mutual circulation could account for monochorial pairs found to be "discordant" in respect to sensory functions.

Finally, a variety of phenocopic effects might be occasioned in monochorial twins, insofar as some of the resulting characters would be hard to distinguish from traits which are largely or entirely due to genetic differences in nontwins. It would seem to follow that monochorial twins should not be included in any study of gene manifestation (e.g., penetrance, expressivity, or specificity as defined by Timoféeff-Ressovsky, 1931) where interest centers on statistical indexes of manifestation for nontwin populations.[8]

[8] There is even doubt that exclusion of individuals or pairs *known* to be of monochorial type would take care of the problem entirely. This review has not attempted to deal with acardii cases or other extreme contingencies in monochorial twinning, but we may note that after Claudius (1859) published his monograph, there was speculation as to whether early derangement and obliteration of one monochorial twin embryo might be a more frequent occurrence than had been supposed. If so, more infants appearing, at birth, to be nontwins might be survivors of monochorial pairs than ordinary examination of secundines would suggest. This possibility was made more plausible by Streeter's detailed account

8. SELECTED RESULTS OF THE TWIN METHOD

When Galton (1875*c*) said the "similar" pairs in the group which he thought comprised the majority of MZ cases were "exceedingly alike in body and mind" (cf. §5, p. 317) he evidently meant that all pairs in this group were very similar in childhood, but not necessarily so in later life.

In twelve of the pairs which he assumed were initially similar (1875*a*, 1876, 1883, and 1907), Galton believed that the effect of illness was marked and "easily to be measured by the present method of comparison." By this he meant that if one twin in the pair had suffered an illness and the other twin had not, the difference which developed between them was attributable to the illness.

In a second group (number unspecified) of the pairs which he assumed were initially similar, Galton saw that intrapair differences developed in later years *despite* the absence of any environmental factors important enough to account for the differences. He attributed these differences to "the tardy development of naturally diverse qualities" or to "characteristics which had lain dormant at first."

With respect to the second group, Galton has been criticized for assuming that there were no important environmental differences simply because none were discoverable in any of the extensive information which he obtained in reply to his questionnaires. But, in retrospect, Galton's perception of the fact that at least some MZ differences were *not* accountable in terms of postnatal factors is perhaps the most remarkable feature of his report. If anything, Galton was more open to criticism (merely on grounds of consistency) in respect to his belief that effects of illnesses were necessarily "great." For he saw that in a third group of initially similar pairs, which he apparently believed was larger than either of the other two groups, "the resemblance of body and mind . . . continued unaltered up to old age, notwithstanding very different conditions of life." This being so, he might have suspected that the illnesses reported to him as reasons for intrapair differences were *not always causes* of those differences, but *effects* of the "dormant" or late-developing traits which,

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(1919) of a case in which the obliteration of one twin embryo was incomplete. His suggestion that a large number of placentas might be studied closely for further evidence on the question does not seem to have been followed, though the association between certain types of tumors in mature individuals and the tendency to twinning in their families has been verified by Edmonds and Hawkins (1941).

The point is, however, that if early obliteration of one monochorial twin were frequent, and if the accompanying disturbances affected reaction rates during embryonic growth of the surviving cotwins of such pairs, it is possible that they would show phenocopic effects. Not being identifiable as twins, they might sometimes enter into manifestation studies even if effort were made to exclude all twins from the sample. Or, aside from manifestation studies as such, it is possible that some syndromes of physical and mental maladies which seem to fit neither genetic nor ordinary environmental hypotheses might have origins of this nature.

as he saw, were the only available explanation of differences in certain other pairs.

Now, some of Galton's cases probably *were* crucial for the question of effects of illness. The difficulty is that no one knows how many of the cases may have been of that kind, and it is hardly safe to assume that all or even most of them were. The question is not whether the illnesses had any effects at all, but whether those effects were, on the whole, as great as they appeared to be. This problem of degree involved in Galton's data exemplifies the problem that has beset twin studies ever since.

Among the authors who have provided reviews of the subsequent studies are Dahlberg (1926), Fortuyn (1932), Rexroad (1932), Guttmacher and Rand (1933), Margolis and Eisenstein (1933), Roberts (1935), K. Conrad (1937), Lotze (1937), Slater (1938), von Verschuer (1939, 1940), Newman (1940*b*), Carter (1940), Essen-Möller (1941*b*), Woodworth (1941), Montagu (1944), Gates (1946), and Stern (1949). It seems appropriate here to review a selection of findings consistent with the inferences drawn in the preceding section of this paper, viz. that after-effects of the mutual circulation may cause a great variety of monochorial twin differences, and may lead to exaggerated accounts of the importance of postnatal factors in general.

Where a study includes a considerable number of MZ twins, and especially in reports concerning pairs found in clinical populations, we may believe that the majority of the MZ pairs were of monochorial type. If, as is here assumed, the intrapair differences are greater in monochorial than in dichorial-MZ cases, then the MZ differences observed in large-scale studies are due mainly to the presence of monochorial pairs among the MZ group; having stated this assumption once, we need not repeat it for each large-scale study discussed.

From the literature on "case reports" or studies involving only one or two MZ pairs, we have selected those reports indicating some degree of "discordance" or intrapair difference. Where it is not known whether or not the cases were of monochorial type, it is here assumed that they probably were; future research will doubtless permit judgment as to how often this assumption may have been mistaken.

Most investigators study a number of different variables or traits in any given pair or group of twins. Desirable as this practice is, the findings are thereby made difficult to review systematically. The categories in which the reports have been grouped below may aid the reader in making certain comparisons of the findings, but that is the only merit that the categories have, and they are by no means mutually exclusive.

Fetal and neonatal anomalies

Adair (1930) studied fetal malformations in 354 plural births with a view to evaluating genetic versus intrauterine environmental factors as causes of the

anomalies. Since his diagnoses of zygosity appear to have been confused his findings need not be detailed, but his assumption that "environmental conditions should act upon monozygotic twins in about the same manner as upon dizygotic" was clearly in doubt. In an important review of the literature on deliveries with one twin blighted, Kindred (1944) found that only 6 of the 48 reports on monochorial cases had stated that placental anastomoses were present; on that basis he concluded that the condition was "not a great factor in blighting."

Szendi (1938*a*) discussed two monochorial pairs in each of which there was a normal infant and a deformed fetus. He believed that in each pair "intrauterine noxa" had affected one fetus and not the other, and that the cases demonstrated the importance of such noxa as causes of congenital malformations in nontwins. Morikawa (1939) and Tsuchiya (1939) studied the hearts and livers of twin pairs that were stillborn or died soon after birth and, independently of Schatz's reports, confirmed his findings that there were marked intrapair differences in the sizes of such organs among pairs of monochorial type.

Reporting a monochorial pair in which one infant showed a condition somewhat resembling pyloric stenosis as the condition is observed in nontwin infants, Lasch (1925) concluded the case indicated that environmental as well as genetic factors were of general significance as causes of pyloric stenosis. Sheldon (1938) reported a discordant monochorial pair in which the condition in the affected twin was even closer to typical pyloric stenosis. Sheldon drew no conclusions.

Reporting a conjoined pair in which only one twin had harelip and cleft palate, Sangvichien (1937) attributed the discordance to an irregularity of "somatic divisions." Morison (1949) alluded to Schatz's work in connection with a discussion of two pairs of grossly discordant monochorial fetuses, but apparently thought that competition of the two fetal circulations "for the utero-placental site" was the point of what Schatz had said. Morison felt that inadequate maternal nutrition to one twin in each pair explained his cases. He said this not only showed "environmental causation" of malformations, but indicated that dietary supplements during pregnancy might effect "some reduction in the incidence of congenital malformations."

Heart defects

Kabakoff and Ryvkin (1934) studied electrocardiographic data on 81 MZ pairs. The discordance found in 10 pairs was thought due to differences in infectious diseases suffered by the individual twins or other postnatal health factors. Similar results were obtained with smaller numbers of pairs by Wise, Comeau, and White (1939), who were interested in whether the electrocardiogram might be useful as an aid in diagnosing zygosity; they decided it was not

since half their MZ pairs were discordant by the criteria they had set. In a third quantitative study of heart functions by Kahler and Weber (1940) the MZ discordances were attributed to differences in the diets, disease histories and psychological environments of the twins.

McClintock (1945) reported a pair of monochorial infants in which one twin had died soon after birth and autopsy had revealed certain defects in its heart. Complications of pregnancy, including indications of hydramnios, had occurred during gestation of the twins. McClintock believed some deficiency in nutrition to one fetus might have caused the anomalous heart condition.

Friedman and Kasanin (1943) gave a detailed account of a 54-year old pair who were clearly MZ, but about whom no information was available as to whether they were of monochorial type. One of the men had been hypertensive for a few years preceding examination, and was found to be suffering from coronary sclerosis. No such condition was discoverable in the other twin; as a boy he had been thought "pre-tuberculous" at one time, but later became slightly stronger physically than his twin. In their study of the twins' life histories, the investigators found no evidence of intrapair rivalry; in fact all reports indicated that the twins were much attached to each other, and had been willing to avoid seeing each other only during a period when their wives were quarreling. However, the investigators noted that certain differences between the twins' personalities were reflected in the reports of their life histories. The possibility that the differences in personality as well as in physical traits could have been prenatally conditioned was overlooked, and it was concluded that the hypertension and coronary sclerosis in the one individual were due to repressed "hostility" which, the investigators assumed, he had developed toward his twin.

Other developmental anomalies

From study of a considerable number of MZ pairs concordant or discordant with respect to clubfoot and related structural variations, Idelberger (1939) concluded that clubfoot was a unit character subject to "strong manifestation fluctuations." Reinhard (1948) reported a monochorial pair in whom only one twin had bilateral clubfoot in marked degree, while an older sibling had bilateral clubfoot in comparatively mild degree. This combination of circumstances led him to question Idelberger's "manifestation" theory, and to doubt the importance of heredity as a factor in clubfoot.

Knauer (1939) reported an MZ pair in whom only one twin had syringomyelia, while two siblings showed the related condition of status dysraphicus. In the light of these findings and earlier reports of MZ pairs discordant for the syndrome, Knauer agreed with other authors that "the twin method fails to a large extent in this disease." Although he recognized the genetic origin of

the syndrome in nontwins, Knauer thought that MZ discordances in it might be due to some peculiarity of the process of MZ zygote formation, such that the process prevented expression of the gene in one twin.

Fowler (1947) reported an MZ pair discordant in respect to otosclerosis. The father of the twins had the disease.

To the reviewer, of course, Knauer's, Reinhard's and Fowler's cases, like the case of Newman and Quisenberry discussed earlier, might be explainable on the assumption that the genes and modifiers were such that the anomaly concerned would not have been expressed ordinarily, but imbalance in the mutual circulation occasioned expression of the character in only one twin.

We may group together five case reports of discordance in general or gross bodily development. A. J. Lewis (1934) reported "atypical" acromegaly in only one twin of an MZ pair aged 46, and indicated that the condition might have been due to an injury to the back of the head which that twin had suffered at age 12. Komai and Fukuoka (1934) described a monochorial pair in whom one twin showed diabetic symptoms and markedly retarded growth after age six, and a relatively small pituitary fossa at age 15. The authors considered a gene mutation or "other haphazard check" on growth as possible explanations. Lemser (1941) reported acromegaly and diabetes which, beginning at age 10, had developed in only one twin of an MZ pair; by age 24 this twin showed a marked hypophyseal tumor. Siemens (1927*a*) noted that one member of an MZ pair examined at age 16 enjoyed the best of health, while the other twin had been suffering since age 10 from severe lateral curvature of the spine; Siemens said this condition was "due to rickets" but gave no further data about the pair's history. Gordon and Roberts (1938) reported a 4-year old pair in whom "the hair and eye color were strikingly similar." Yet only one twin was paraplegic and they differed markedly in the degree to which they showed mongoloid traits. These and other considerations led the authors to think the twins' zygosity must be DZ rather than MZ. Later, Roberts (1947) stressed that MZ pairs show "non-inherited differences determined in some way we do not yet understand."

Lenz (1935) discussed certain female MZ pairs in whom one twin appeared to be less feminine in features and disposition than the other. Lenz believed the differences might be due to what he termed "reciprocal disturbances" in such pairs during prenatal life. Szendi (1939) reported two pairs of conjoined fetuses; in each pair one fetus showed markedly aberrant development of the sex organs.

The literature contains other reports of MZ differences in respect to primary sex characters, but only the conjoined pair reported by Feldman (1937, p. 377) and the monochorial pair described by Guldberg (1938) appear to have been well ascertained so far as zygosity was concerned. The problem dates from the remarkable monograph by Numan (1844) on the freemartin in cattle, which

contains references to possible "freemartin" effects in pairs of cattle that were supposedly both males. Partly in connection with Numan's remarks and partly from more or less erroneous observations of his own, Hart (1912, 1918) developed the idea that MZ twinning occasioned the freemartin condition. Lillie (1917, 1923) disposed of Hart's theory. There remains, however, the possibility that in some cases disturbances in the mutual circulation of monochorial human fetuses may affect the expression of sexual characters, as suggested by the reports of Lenz and Szendi. If such effects occur they should, of course, be considered a different kind of phenomenon than either the freemartin effect or the "mosaic" effect discovered by Owen (1945). (C. G. Hartman, 1920, at first thought that freemartin effects occurred in human DZ pairs, but in a later article by Hartman and League, 1925, he did not support this view).

Sensory traits and certain diseases

Nettleship (1912) gave a detailed account of an assuredly monochorial pair of girls, one of whom had become aware at age six that her twin could not "tell the colors" properly. When tested at age nine, the normal twin could differentiate hues throughout the full range of the spectrum; the other girl could identify only red and dark blue reliably. Nettleship noted there was no measurable difference between the two eyes of either twin, and thought the intrapair difference was accountable only in terms of "some cause acting at an extremely early stage of the embryo." Dahlberg (1926) believed the case consistent with his theory regarding effects of lateral inversions in MZ pairs. Stocks and Karn (1933) reported an "apparently" MZ pair in whom only one of the girls was red-green colorblind.

Ardashnikov *et al.* (1936) reported two MZ pairs discordant with respect to tasting phenyl-thio-urea, and Rife (1938*a*) found five more cases of the same kind. G. Hartmann (1939) expressed the opinion that such cases reflected faulty techniques of measuring the twins' taste thresholds. She believed that certain small phenotypic differences were to be expected within MZ pairs as a result of effects of lateral inversions, but thought these differences would not be great enough to consider one twin a taster and the other a non-taster if their reactions were measured accurately and if the "threshold" or dividing line between the tasters and non-tasters were properly chosen. Later work may show what proportion of apparently discordant MZ cases are explainable in terms of faulty measuring techniques; but if all of them are not, there would seem to be no more reason to attribute such cases to effects of lateral inversions than to after-effects of the mutual circulation.

With respect to occlusion of the jaws and certain other dental conditions, there may be substantial reasons for the common belief that lateral inversions are major causes of MZ discordances, but one may suspect that MZ differences in the extent of caries development are more often due to after-effects of im-

balance in the mutual circulation. Important studies of dental conditions in twins have been reported by Cohen, Oliver, and Bernick (1942), Dahlberg and Dahlberg (1942), Brucker (1944), W. L. Wilson (1946), and Lundström (1948). The report of Lundström included a comprehensive review of pertinent literature. He noted that intrauterine environmental factors vary more for MZ than for DZ pairs "due to anastomosing," but otherwise Lundström, like the earlier authors, gave attention exclusively to lateral inversions, natal factors, and postnatal influences as causes of MZ differences.

In the first of the four large-scale studies of tuberculosis in twins, Diehl and von Verschuer (1933) summarized Schatz's data to the effect that monochorial pairs with the greatest differences were usually aborted early or born prematurely, so that "at term there remain only [monochorial] pairs with small differences . . . and the great influence of vascular connections is masked" (Schatz, 1887*a*). Having considered Schatz's observations to that extent, Diehl and von Verschuer gave no further attention to the problem of prenatally conditioned differences, and neither did Uehlinger and Künsch (1938) nor the authors of the other two major studies of tuberculosis in twins. Kallmann and Reisner (1943*a*, *b*) decided that their results showed that resistance to tuberculosis was conditioned by a multifactorial genetic mechanism, and Vaccarezza and Dutrey (1944) believed their data showed that genetic factors were very important in the course of the disease but not in "the acquisition of the bacillary infection."

Each of these studies included over a dozen MZ pairs in whom one or both twins were tuberculous, and all four studies provided evidence that genetic factors are significant causes of susceptibility to the disease. The difficulty, from the reviewer's standpoint, is that these investigations probably underestimated the importance of genetic factors in tuberculosis among people in general. If so, health departments and organizations working to combat the disease have been made that much less aware of the need for reckoning with individual differences in susceptibility, with corresponding inefficiencies in the work.

A careful though largely qualitative study of MZ concordance and discordance in respect to allergic tendencies was reported by Spaich and Ostertag (1936). They found that concordance was relatively marked for hay fever, intermediate for migraine and uticaria, and low for asthma. It is possible that this order reflects the relative degrees of genetic determination of the allergies in nontwin populations, but on the other hand the results might represent only the degrees to which such allergies are affected by disturbances in the mutual circulation; and, on the whole, the allergies may be more genetically determined in the general population than would appear from the twin data. Creip (1942) studied effects of "passive transfer" tests on seven MZ pairs. The results indi-

cated more resemblances than differences in the pairs tested; the differences were attributed to "variations in exposure and contact."

Bossik (1934) studied affections of the lymphatic system in 130 MZ pairs. The discordances were difficult to summarize statistically, but they were frequent in the group as a whole, and were interpreted as showing "predominant influence of environment," although genetic factors were considered to be important also. Faxen (1935) reported two pairs that were probably monochorial, and both were discordant in respect to hyperthyroidism. Faxen decided they must have been DZ, since to think them MZ "would upset all our previous conceptions," he said.

Romanus (1947) reported a 43-year old MZ pair in whom only one twin had suffered from psoriasis since age nine. Romanus noted that at least five other MZ pairs had been reported as discordant in respect to this disease, as compared with 18 MZ pairs concordant for it; he believed the discordant cases were due to effects of lateral inversions.

Neurological and psychiatric studies

Jenkins and Glickman (1934; see also Jenkins, 1935) reported a pair of MZ girls in whom choreo-athetoid movements, moderate dullness, and a reticent personality characterized only one twin. Since the mother's report of that twin's birth indicated a difficult delivery, it was concluded that a brain injury at birth probably accounted for the intrapair difference. Analogous circumstances in the deliveries of two more pairs showing neurological differences were reported by Bradway (1937). Both pairs were of monochorial type. Bradway noted that they were inconclusive for the question of birth injury owing to "the possibility of physical dissimilarity in monozygotic twins."

Kasanin (1934) discussed an MZ pair who were reportedly very similar up to age 18. After that their environments changed; one twin became a successful mechanic while the other undertook to be a writer and was unsuccessful. The mechanic remained mentally stable and the other twin developed schizophrenia. Kasanin granted that there may have been "some slight difference" between the twins before age 18, but believed the one twin developed schizophrenia because he "had to find a solution of his failure in a psychosis."

Paterson (1949) considered the possibility that the mutual circulation and other conditions may have played some part in the life histories of an MZ pair discordant for hysteria, but felt that "excessive attachment . . . played a dominant role" in the affected individual, who "might never have become an hysteric if she had not been born a twin." In connection with a monochorial pair discordant in epileptic tendencies, W. Freeman (1935) held that intrapair rivalry was not an important factor; his discussion of alternative factors that might have occasioned the difference was not clear to the reviewer.

Reed (1935) reported an MZ pair in whom only one twin developed schizophrenia and tuberculosis, while Critchley (1939) studied a pair in whom one twin suffered several periods of unconsciousness per day while the other showed only minor tics of eye and mouth muscles; neither Reed nor Critchley drew conclusions from their cases. Hobbs (1941) discussed five MZ pairs who were more or less discordant with respect to neuropsychiatric traits. He remarked that "there is the intrauterine period of which we know nothing," but believed that the discordances in four of the five pairs were attributable to natal or postnatal factors. Craike, Slater, and Burden (1945) studied an MZ pair aged 54 who had been separated most of their lives. One twin had shown only infrequent paranoid symptoms, while the other's history was one of "chronic insidiously progessive paranoia." The difference was thought attributable to the less fortunate upbringing of the more affected twin.

Kallmann (1941) explained the fact that he had found 12 of 57 MZ pairs discordant in respect to schizophrenia as due either to "strong constitutional resistance" or to the "absence of furthering dispositional factors" in the unaffected members of the 12 pairs. In a more complete report (Kallmann, 1946) he found that 54 of 174 MZ pairs were classifiable as discordant with respect to the psychosis. This meant a discordance "rate" of 31%, and when he grouped the pairs according to similarity or dissimilarity of the respective cotwin's environmental circumstances, the discordance rate varied *only* from 29% to 35%. This form of statement oversimplifies his findings to some extent; the reader should consult the details of Kallmann's own analysis, which seem careful and thorough to the reviewer except for the conclusions. Kallmann believed his data showed that expression of the genetic factor or factors causing schizophrenia could be prevented in the individual provided that "the psychosomatic elements, which may act as predispositional, precipitating, or perpetuating agents in such a psychosis, are morphologically identified, and that the complex interplay of etiologic and compensatory mechanisms is fully understood." If the reviewer understands this conclusion, it means the discordant MZ pairs suggest that, in nontwins as well as twins, there may be ways of offsetting the development of schizophrenia in the individuals who are predisposed to the psychosis. This view may be justified on other grounds, but it would seem that before we rely on twin data for further information about the disease and possible ways of treating it postnatally, we need to learn how often it may be expressed differently in monochorial pairs for reasons that have little to do with postnatal environmental factors.

In an intensive study of the life histories of 21 MZ pairs, among whom one or both twins in each pair had been sufficiently disturbed to require institutional care, Essen-Möller (1941*b*) reported a variety of intrapair differences as well as similarities in psychiatric functions. Of the natal or postnatal environmental factors which might have caused the differences, Essen-Möller found

that "only a few appear to be plausible." He was led to conclude that the important environmental causes of the observed intrapair differences were probably operative "early in ontogenesis."

Psychological studies

Newell (1930) found marked differences in the mental abilities and personalities of an MZ pair aged 14, and believed the differences were due mainly to "encephalitis, polioencephalitis, or a cerebral form of poliomyelitis" which one twin had reportedly suffered at age two. Misbach and Stromberg (1941) administered the Rorschach (ink-blot) test to an MZ pair in whom one twin had developed a speech disability following an illness. The results were said to show "the dynamic properties of the social field which in many, or perhaps in all cases, produce divergences in development of twins as well as between siblings reared together."

Burnham (1940) studied two MZ pairs showing certain intrapair differences in intelligence and personality. The disease histories of the twins were apparently not of much interest, and Burnham concluded that the intrapair differences were due to "small, almost intangible environmental differences." Geyer (1940) observed 30 MZ pairs over a two-year period and noted certain "basic" intrapair differences in their personalities which were taken to mean that the role of heredity in personality differences was, in general, rather limited.

Blatz and Millichamp (see Blatz *et al.*, 1937) studied the intra-set differences in behavior among the Dionne quintuplets, and found the differences too consistent to be attributable to random variations or errors of observation. To explain the differences, the investigators said (p. 11) that "the occurrence by chance of a unique response starts a divergence of environmental influence which grows wider as the child grows"; and at another point (p. 21) the findings were said to show that a person's social behavior was "conditioned largely by the social environment." Later, MacArthur and Dafoe (1939) discussed possible after-effects of the mutual circulation and natal factors, declaring that they might well have been the causes of the differences among the quintuplets in "leadership, originality, aggressiveness, attitude toward authority, and social interests."

In a discussion of certain aspects of research with twins, Zazzo (1940) gave a brief description of effects of the mutual circulation in monochorial fetuses. He doubted that the effects were lasting in mature pairs, and, as examples of the kinds of factors which he believed were typical causes of MZ differences in psychological traits, he mentioned "fatigue, alcoholism, and syphilis."

Quantitative studies of psychological functions in twins include the investigations of Merriman (1924) and Herrman and Hogben (1932) on intelligence; of McNemar (1933) on motor skills; of Brody (1938) on mechanical ability; and of Cattell and Molteno (1940) on temperament. All of these studies were

very valuable so far as they went, but none of the investigators noted that the obtained MZ differences might give an exaggerated impression of the importance of environmental factors so far as nontwin groups were concerned.

Carter (1932) intensively studied three MZ pairs in whom, though the twins in each case had been reared together, there were marked intrapair differences. He also took account of Koch's (1927) detailed report on a conjoined pair showing marked differences. Carter pointed out that in none of these pairs could the observed differences be reconciled easily with environmental conditions ordinarily thought to be important. "At least," he said, "a consistent explanation in terms of such environmental factors is elusive." He went on to note that the data on the four pairs "undoubtedly have some bearing" on studies of MZ twins reared apart. At that time Muller (1925) had published a full account of the pair discovered earlier by Popenoe (1922), and several of the pairs discussed below had been reported.

In connection with their studies of 19 pairs of MZ twins reared apart, Newman, Freeman, and Holzinger (1937, p. 38) held that after-effects of the mutual circulation in monochorial pairs were "too important to be ignored." Largely for this reason Newman (p. 356) believed that the "excess" differences observed within the pairs reared apart, as compared with the differences observed within MZ pairs reared together, were the fairest measure of postnatal influences. Reasonable as this measure would seem, it could involve exaggeration of the net effect of postnatal factors in case there were some degree of "selective placement" of the separated twins.

For this to have happened, the healthier-seeming infant need not *always* have been the twin who was placed in the better home (and indeed it appears from the case reports that the opposite probably happened in one or two pairs). Yet if placement of the individual twins was "selective" more often than otherwise, the over-all results of the study give an exaggerated picture of effects of postnatal factors.

Retrospective reports on the placements of such pairs are scarcely reliable guides to all of the circumstances involved, if only because there may be some tendency to euphemize the facts, particularly where a difference in the health of the twins appears to be significant to any of the adults having a choice in the matter. No one knows, of course, whether placement of individual twins is or is not selective in a disproportionate number of cases. That being so, however, it hardly seems safe to say (as did Newman, Freeman, and Holzinger, p. 358) that such intrapair differences as are of prenatal origin "could have only a fortuitous relation" to the levels of environment in which separated twins spend their childhood and adolescent lives.

Thus few pairs of MZ twins reared apart can be said to satisfy the requirements of "twin-control" experiments. The reared-apart cases are of interest and value, but they have not yet yielded as much definite information on effects

of training as that already obtained in the well controlled studies which Gesell and Thompson (1929) initiated on one pair. Moreover, it is doubtful that even a hundred more reared-apart pairs like those studied so far would provide data comparable with that potentially available from the investigations proposed by Blakeslee and Banker (1930) and F. N. Freeman (1941).

9. CONCLUSION

Over the past 75 years nature-nurture studies of twins have served to demonstrate minimal effects of genetic variation, but even that purpose has probably been defeated to a large extent by the biases inherent in the twin method.

With respect to any one case report where an observed MZ difference has been thought due to an environmental factor of a kind believed important among nontwins, it is impossible to say whether or not the investigator's judgment of the meaning of the MZ difference was correct in that particular case. Yet when such case reports as a whole are considered together with indirect evidence bearing on the problem, it seems certain that the interpretations given the case reports have tended to exaggerate the effects of postnatal environmental factors. With respect to statistical studies of large groups of twins, it is fair to assume that the interpretations given the findings have been about as mistaken, in kind, as the inferences drawn from case reports; the statistical studies may have been less mistaken in degree, but if so, it is mainly because they have included a higher proportion of dichorial-MZ pairs than the case reports.

It would seem to follow that a part of the time and effort which will doubtless be expended on research with twins in the next decade or two could well be spent on identifying twin pregnancies two months or more before term, and obtaining much more complete information than we now possess as to effects of prenatal and natal factors in the two types of MZ pairs.

The results of such a study might show that the twin method, as ordinarily applied, is too crude for purposes of modern nature-nurture studies. At the same time, pairs of monochorial type might prove to be of more interest and value for theoretical problems of developmental genetics than is commonly supposed. And for purposes of studying effects of postnatal environmental factors, there is little that one could hope to learn from studies using the ordinary or uncontrolled twin method which could not be learned at least as well from carefully designed "twin-control" tests employing selected MZ pairs.

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Note: To save the space and expense which a full bibliography would require, a mimeographed list giving full titles of these and many further pertinent references has been prepared and is available upon request to the author.

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Determination of the Zygosity of the Waddington Quintuplets Born in 1786

NORMA FORD WALKER

Department of Zoology, University of Toronto, Toronto 5, Ontario, Canada

SINCE quintuplet births to date number only about 53 authentic cases, it is of interest to determine whenever possible the type of twinning involved in these higher multiple sets and particularly in those sets which may have been derived from a single ovum in which the continued twinning of the young embryo has resulted in five like-sexed sibs. Many more than 53 quintuplet births certainly have occurred, but adequate accounts of them are not on record or else early records have not been rediscovered. A summary of 45 cases is given by MacArthur and Ford (1937) and eight more are to be found in later papers (Ford & Caruso, 1938; Rau, Aiyar & Mathew, 1940; Keettel, 1941; Olivella & Vega, 1941; Filho, 1942; McDaniel, 1943; Associated Press, 1950).[1]

None of the infants of these sets lived, until the Dionnes were born in Canada in 1934. Only a few of the sets have been preserved, such as one set in the Dublin Hospital in Ireland (Kennedy, 1839), one in the Medical College of the Tokyo Imperial University in Japan (Sato & Sato, 1902), one in the Army Medical Museum in Washington (Hibbs, 1896), one set at Duke University Hospital, Durham, North Carolina (Hamblen, Baker & Derieux, 1937) and the two sets here described belonging to the Royal College of Surgeons of England.

One of the latter sets, the Waddington quintuplets, was born in 1786 in Lower Darwin, Lancashire, England and is the eighth authentic case. The earliest case occurred in 1566 (McDaniel), followed by those in 1694 (Harder & Schwallerus), 1719 (Müllerheim), 1736 and 1739 (Gentleman's Magazine), 1743 (Vogt), and 1771 (Shishido). An account of the birth of the Waddington quintuplets was read before the Royal Society of London in 1787 by Garthshore.

The second set of quintuplets, also sent to me by the Royal College of Surgeons, consisted of five girls, born in 1877 (Farre). The suspicion of the curators that one of the fetuses had been lost and later substituted[2] is in our opinion

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[1] The author acknowledges the kind assistance of Dr. Beatrice Corrigan for the translation of Spanish and Portugese papers.

[2] To the original entry in the catalogue is added by Sir William Flower the following note: "I believe that the top foetus to the left side (with the band around the right ankle) does not belong to this litter, but was substituted for one that was accidentally lost. The others are all correct. *W. H. F.*"

well founded, owing to the larger size and more advanced development of the substituted fetus, even though the fetuses are too young for a study of dermal configurations, being between two or three months in development.

The author wishes to express her thanks to Dr. John Beattie, conservator of the Royal College of Surgeons of England, to the Hon. and Rev. H. J. Cody, president emeritus of the University of Toronto, and to the Rt. Hon. Mackenzie King, formerly Prime Minister of Canada, who jointly arranged for the safepassage of these specimens to the University of Toronto where they were housed during the Second World War.

BIRTH AND PLACENTA OF THE WADDINGTON QUINTUPLETS

The birth of the Waddington quintuplets was attended by Dr. Hull. The infants, five girls, were born prematurely at five months of development, to a mother aged 21 years at her second pregnancy. Two were born alive, one was still-born, and two were macerated. The living children survived but a short time. Dr. Hull was allowed by the parents to take the fetuses, which he preserved and later sent to the Hunterian Museum of the Royal College of Surgeons, but because of the superstitions of the Lancashire people concerning birth membranes, Dr. Hull was not allowed to have the placenta. He made, however, a careful examination and his description can be interpreted as a monochorionic placenta with five amnia. This type of placenta is the one most likely to occur with a one-egg set, although fewer amnia may be present and more than one chorion may be associated with a uniovular multiple set.

SEX RATIO IN QUINTUPLETS

The sex of the Waddington quintuplets raises a point of interest. The sex ratio of females to males increases in multiple sets from twins to quadruplets. The number of females per 100 males has been calculated to be 94 in single births, 97 in twins, 101 in triplets and 109 in quadruplets (Walker, 1947). One would expect that in quintuplet sets the females would again be in the majority and it may be due to the paucity of data that in the 49 recorded cases in which the sex of all infants is given the ratio is only 85.6 females to 100 males.

LENGTH AND WEIGHT

In length, four of the Waddington quintuplets measured about 9 inches, one about 8 inches. In weight the smallest was a quarter pound, the two largest more than a half pound. In comparison, the Dionne quintuplets at birth had an average length of 13 inches and an average weight of 2 pounds, 11 ounces.

DERMAL CONFIGURATIONS

The only method of determining the zygosity of a preserved set such as the Waddington quintuplets is by the analysis of the dermal configurations oc-

curring on the fingers, palms and soles. These patterns, which are known to be inherited are permanently established during the third and fourth fetal months. The variations of the configurations depend upon the interaction of the developing dermal ridges and the receding fetal mounds (Cummins & Midlo, 1943).

The dermal patterns of the Waddington quintuplets were studied both by direct observations under a binocular microscope and from numerous photographs made by Mrs. Audrey Shortt to whom I am much indebted for her great patience and skill in executing this difficult task.

The ridges of the three non-macerated fetuses were at first obscured by the firm cheesy covering, the vernix caseosa. In these specimens the ridges were exposed by carefully and gently rubbing away the firm covering with small triangles of moist blotting paper. To assist in softening, a few drops of dioxane or oil of wintergreen or absolute alcohol were used. The clearing of the ridges was at all times followed under the binocular microscope and the process demanded the same care that a paleontologist uses in clearing a fragile fossil embedded in rock.

On the two macerated fetuses (Nos. 3681-2 and -5) the cheesy covering was loose and had either peeled off or was hanging in shreds. The exposed dermal ridges were very clear, their form and height accentuated by the shrunken condition of the skin.

Before photographing, the skin was flooded with absolute alcohol and then dried quickly with an electric fan. A slight temporary shrinkage brought up the dermal ridges.

DIGITAL PATTERNS

Digital patterns and ridge counts could be determined for some fingers but for others it was impossible either because of the very shrunken condition of the two macerated specimens or because of the close adherence of vernix to the tiny digits of the other three individuals. Descriptions of digital patterns have therefore been omitted.

PALMAR PATTERNS

The average length of the hands, including palm and fingers, was about one inch. The extreme difficulty of photographing the dermal ridges and particularly of arranging the light to catch the edges of these ridges made it impracticable to keep the photographs to the same scale. There is, therefore, considerable variation in the size of the photographic reproductions.

The palmar outlines (fig. 1) were traced directly from photographs (plates I-III) and hence are shown *in reverse* of the customary palmar diagrams. The latter are made from palmar prints and the print of a hand is the mirror-image of the photograph of the hand.

The dermal configurations were outlined and formulated according to stand-

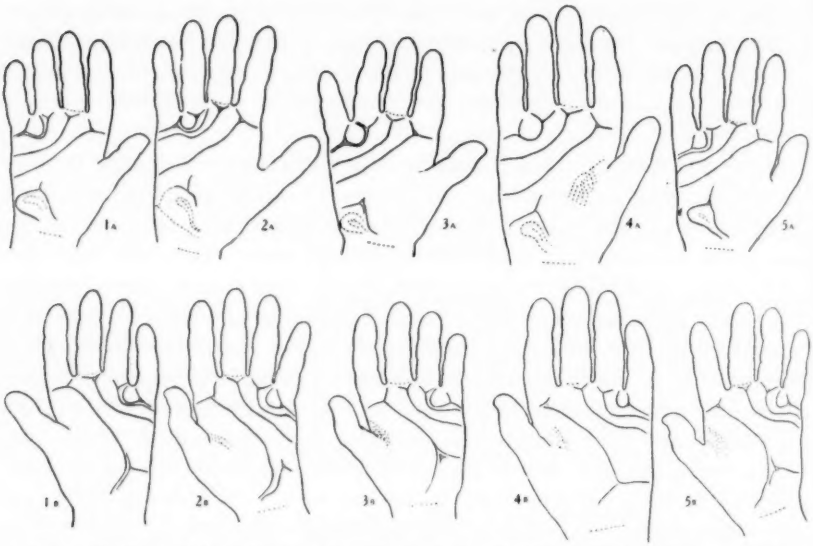

FIG. 1. Outlines of the palmar configurations of the Waddington quintuplets. 1A and 1B right and left palms of No. 3681 (1); 2A and 2B of No. 3681 (2); etc.

TABLE 1. PALMAR FORMULAE OF THE WADDINGTON QUINTUPLETS

MUSEUM NUMBER	LINEAR FORMULA				AXIAL TRIRADII	PATTERN FORMULA				
	D.	C.	B.	A.		Hypo.	T/I_1	I_2	I_3	I_4
Left Palms										
3681(1)	7(8)	5″(6)	5′	1	t′(31.5)	A^u/A^e	0	0	0	L
3681(2)	7	5″	5′	1	t′(28.3)	A^u/A^e	V/0	0	0	L
3681(3)	7	5″	5′	3/1(2)	t′(36.8)	A^u/A^e	V/V	0	0	L
3681(4)	7	5″	5′	3/1	t′(28.1)	A^u/A^e	V/V	0	0	L
3681(5)	7	5″	5′	1	t′(29.4)	A^u/A^e	V/V	0	0	L
Right Palms										
3681(1)	7(8)	5″(6)	5′	4	t′(33.3)	A^u/L^e	0	0	0	L
3681(2)	9(8)	7 (6)	5″	4	t′(38.8)	A^u/L^e	0	0	0	L
3681(3)	7(8)	5″(6)	5′	5′	t′(29.7)	A^u/L^e	0	0	0	L
3681(4)	8	6	5″	4	t′(32.5)	A^u/L^e	V/0	0	0	L
3681(5)	7	5″	5′	4	t′(36.1)	A^u/L^e	0	0	0	L

Symbols: A^u, arch ulnar; A^e, arch carpal; L^e, loop carpal; V, vestigial; Hypo., hypothenar; T/I_1, thenar and first interdigital; I_2, second interdigital, etc.

ard methods (table 1) and homolateral differences calculated. The use of dermal patterns is an extremely objective method of analysis, in which lines are traced from recognized triradii to their marginal terminations. The directions of these

TABLE 2. HOMOLATERAL DIFFERENCES IN THE MAIN LINES AND PALMAR PATTERNS OF THE WADDINGTON QUINTUPLETS, COMPARED WITH THE AVERAGE DIFFERENCES FOR TWINS

SETS COMPARED	MAIN LINES AND AXIAL TRIRADII		PALMAR PATTERNS	
	Average Difference ±S.E.	Standard Deviation	Average Difference ± S.E.	Standard Deviation
Waddington quintuplets (10 pairs)	10.7 ± 1.9	6.1	3.5 ± 0.6	2.0
Monozygotic twins (53 pairs) (Walker, 1950)	17.6 ± 1.4	10.0	21.4 ± 1.8	12.8
Dizygotic twins (20 pairs) (Walker, 1950)	31.5 ± 2.2	9.6	32.0 ± 8.9	15.8

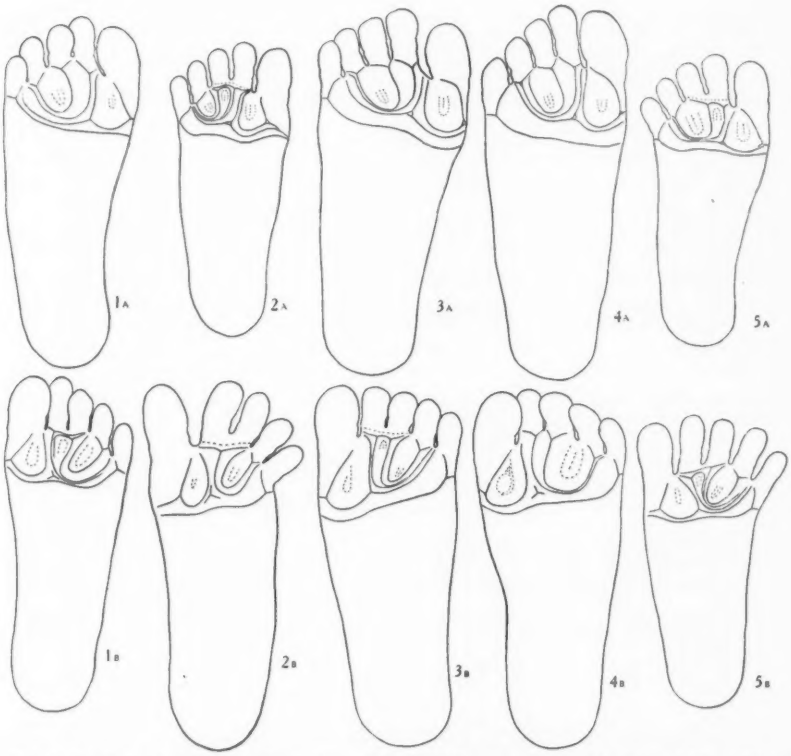

FIG. 2. Outlines of plantar configurations of the Waddington quintuplets. 1A and 1B right and left soles of No. 3681 (1); 2A and 2B of No. 3681 (2); etc.

main lines and the patterns of recognized areas are then formulated and the differences compared.

Homolateral differences in the main lines and triradii for the Waddington

quintuplets, compared among themselves as ten sets of twins, amounted to an average difference of 10.7 per cent, compared with average differences of 17.6 for monozygotic twins and 31.5 for dizygotic twins (table 2). Homolateral differences for palmar patterns of the Waddington quintuplets amounted to

TABLE 3. PLANTAR FORMULAE OF THE WADDINGTON QUINTUPLETS (ALTERNATE FORMULATIONS OMITTED)

MUSEUM NUMBER	LINEAR FORMULA					PATTERN FORMULA						
	D.	C.	B.	A.	Hal.	Hypo.	Calcar	Then. (1).	Then. (2)/I1	I2	I3	I4
Left Soles												
3681(1)	15	9	7	7	13	0	0	0	$0/L^dy$	L^{pd}	L^d	0
3681(2)	15	9	7	0	13	0	0	0	$0/L^dy$	c	L^d	0
3681(3)	15	9	7	7	13/7	0	0	0	$0/L^dy$	L^{pd}	L^d	0
3681(4)	15	10	8	7	13	0	0	0	0/Wy	0	L^d	0
3681(5)	15	9	7	7	13/7	0	0	0	$0/L^dy$	L^{pd}	L^d	0
Right Soles												
3681(1)	15	10	8	7	13/7	0	0	0	$0/L^dy$	0	L^d	0
3681(2)	15	9	7	7	13	0	0	0	$0/L^dy$	L^{pd}	L^d	0
3681(3)	15	10	8	7	13	0	0	0	$0/L^dy$	0	L^d	0
3681(4)	15	12	9	8	13	0	0	0	$0/L^dy$	0	L^d	0
3681(5)	15	10	8	7	13/7	0	0	0	$0/L^dy$	L^{pd}	L^d	0

Symbols: L^d, loop distal; L^{pd}, loop proximal, turning distally; W, whorl; 0, absence of pattern; y, proximal triradius. ———, fusion of digits.

TABLE 4. HOMOLATERAL DIFFERENCES IN THE MAIN LINES AND PLANTAR PATTERNS OF THE WADDINGTON QUINTUPLETS, COMPARED WITH THE AVERAGE DIFFERENCES FOR TWINS

SETS COMPARED	MAIN LINES		PLANTAR PATTERNS	
	Average Difference ± S.E.	Standard Deviation	Average Difference ± S.E.	Standard Deviation
Waddington quintuplets (10 pairs)	15.0 ± 3.2	10.0	14.0 ± 2.0	6.3
Monozygotic twins (51 pairs) (Walker, 1950)	32.1 ± 2.7	19.0	32.7 ± 2.2	15.9
Dizygotic twins (20 pairs) (Walker, 1950)	66.0 ± 8.9	39.9	62.5 ± 4.6	20.5

3.5 per cent, compared with 21.4 for monozygotic twins, and 32.0 for dizygotic (table 2).

PLANTAR PATTERNS

Plantar outlines and photographs are given in figure 2 and plates III-IV, the formulae and homolateral differences in tables 3 and 4. The average differences for the Waddington quintuplets for both main lines and patterns fall

well below the averages for monozygotic twins, being 15.0 and 14.0, compared with 32.1 and 32.7 per cent. The homolateral differences for dizygotic twins are much higher, namely 66.0 and 62.5 per cent.

CONCLUSIONS

The main conclusion drawn from the analyses of the palmar and plantar configurations is that the Waddington quintuplets are a monozygotic set. The description of their placenta supports this diagnosis. Previously for only two other sets have there been sufficient data to make a diagnosis of monozygosity, namely for the Dionne quintuplets (MacArthur & Ford, 1937) and the set studied at Duke University (Hamblen, Baker, & Derieux, 1937).

SUMMARY

1. The palmar and plantar configurations of the Waddington quintuplets born in 1786 have been studied both by direct observation and by means of photographs of the dermal ridges.

2. The homolateral differences for the dermal configurations of these quintuplets, compared among themselves as ten sets of twins, showed in each instance an average difference lower than the difference for monozygotic twins and much lower than that for dizygotic twins. Hence the dermatoglyphic evidence indicates that the set was derived from one zygote (monozygotic).

3. The description of the placenta, monochorionic, with five amnia is in keeping with this diagnosis.

4. Among 53 authentic cases of reported quintuplet births the Waddingtons are the third set to be classified as monozygotic.

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PLATES I–IV

Norma Ford Walker
Determination of the Zygosity of the Waddington Quintuplets Born in 1786
Am. J. Human Genet., Volume 2, number 4, 1950

PLATE I. Waddington Quintuplets. Right (1A) and left (1B) palms of fetus no. 3681(1); right (2A) and left (2B) palms of fetus no. 3681(2). Scales = 5 mm.

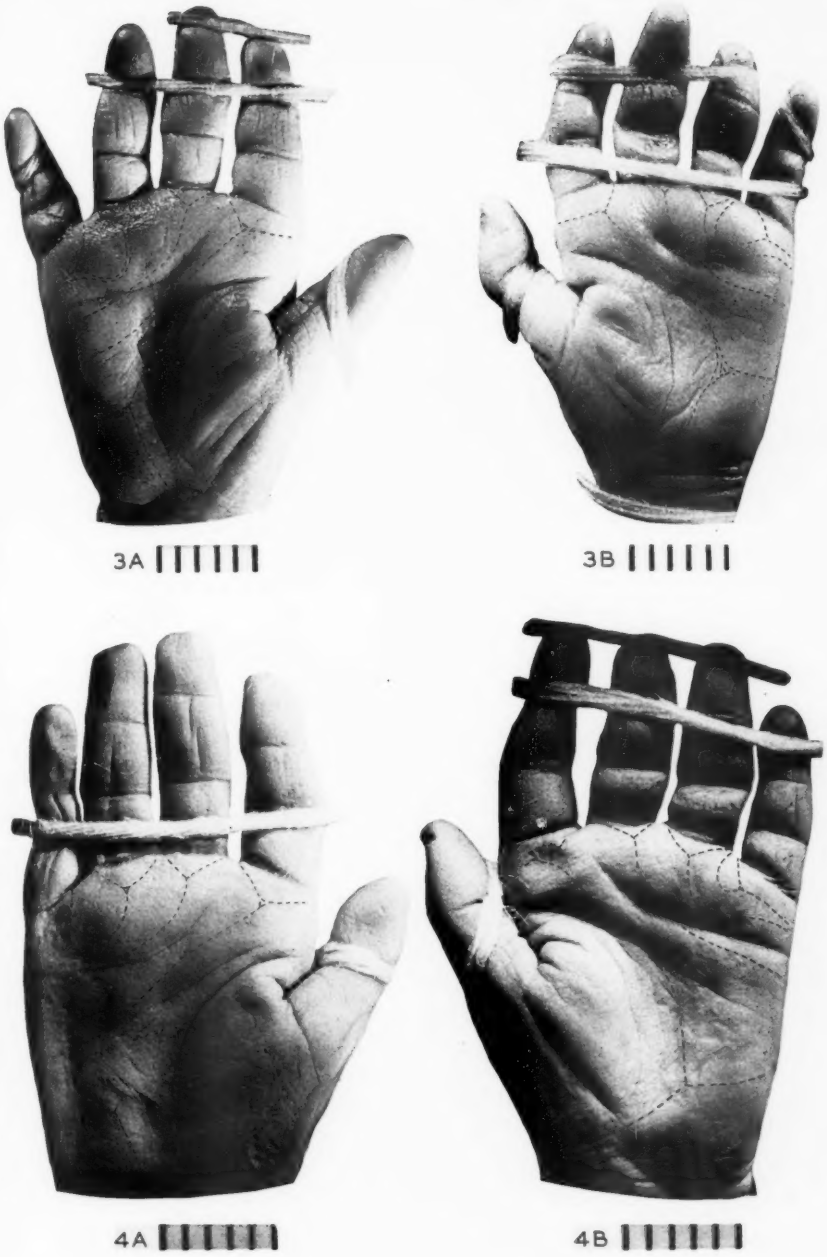
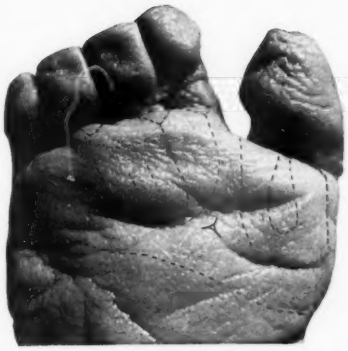
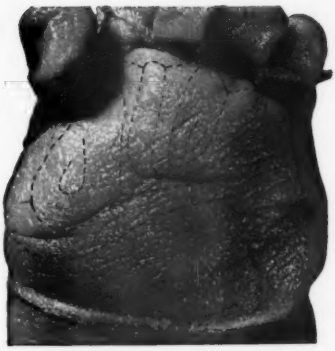


PLATE II. Waddington Quintuplets. Right (3A) and left (3B) palms of fetus no. 3681(3); right (4A) and left (4B) palms of fetus no. 3681(4). Scales = 5 mm.

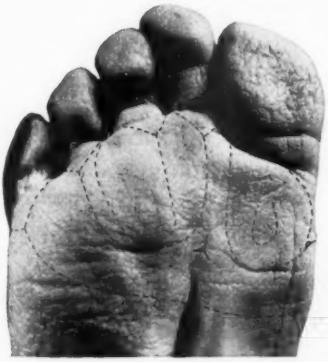
PLATE III. Waddington Quintuplets. Right (5A) and left (5B) palms of 3681(5); right (1A) and left (1B) soles of 3681(1); right (2A) and left (2B) soles of 3681(2). Scales = 5 mm.



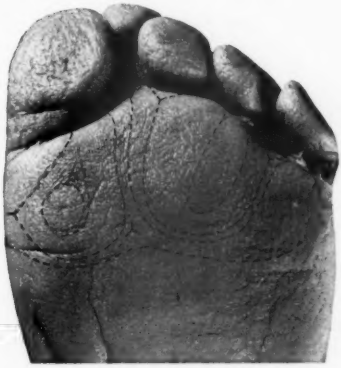
3A



3B



4A



4B

5A

5B

PLATE IV. Waddington Quintuplets. Right (3A) and left (3B) soles of 3681(3); right (4A) and left (4B) soles of 3681(4); right (5A) and left (5B) soles of 3681(5). Scales = 5 mm.

Situs inversus, Asymmetry, and Twinning

JOHAN TORGERSEN

Department of Mass Roentgenography, Norwegian Health Department, and the Anatomical Institute, University of Oslo, Norway

INTRODUCTION

THE relation of situs inversus to twinning has attracted much attention from experimental embryologists. Thus, Spemann and Ruud (1922) produced situs inversus by division of the amphibian egg, the twin derived from the right half frequently showing situs inversus. Komai (1938) observed situs inversus in the salmon, particularly in one partner of conjoined twins and relatively frequently in the smaller twin.

Naturally students of human twins have been interested in situs inversus in connection with the general problem of mirror-image asymmetry in twins. The relatively great dissimilarity observed in some human twins discordant for situs inversus has been considered as evidence of a mirror-image mechanism, the dissimilarity being supposed to be an indicator of the bilateral differentiation at the time when the division took place (Dubreuil-Chambardel, 1927; Cockayne, 1939; Helweg-Larsen, 1947). However, it can hardly be excluded that both the dissimilarity and the inversion in these cases are due to causes having no relation to the division or a mirror-image mechanism. In this connection, it is noteworthy that Mattison (1933) found only 1.3 per cent twin births among a total of 615 births occurring in the families of 4 individuals with situs inversus, compared with a frequency of 1.5 per cent twin births in Sweden generally.

As this problem is a fundamental one in twin research, the following data which have been collected in a rather extensive study of situs inversus in Norway may be of interest.

THE MATERIAL

The material includes 270 cases of situs inversus observed during a 7 year period, 1944–1950. During this time the interest of the author has focused on various aspects of the problem. In the earlier years, attention was directed to the relation between situs inversus and other anomalies, particularly to abnormalities of the lungs, nose, lower jaw, spine, and heart. These problems have been dealt with in a series of papers (Torgersen, 1946–1950).

Most of the cases of situs inversus have been discovered in mass x-ray photography of the Norwegian population. In some regions of the country, having

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a total population of about 1,000,000 approximately 90 per cent of the inhabitants over 15 years of age have been examined. Up to the present time, 200 cases of situs inversus have been discovered among 1,800,000 individuals above 15 years of age. The frequency is thus 0.011 per cent, or slightly over 1 per 10,000.

The 70 additional cases have been discovered through hospitals and municipal health departments. These cases are most probably derived from regions of the country not thoroughly covered by the populational surveys or represent children younger than 15 years. Assuming the same frequency within these less extensively sampled portions of the population, one would estimate that the total Norwegian population of 3,100,000 persons contains about 340 cases of situs inversus.

In the miniature radiogram the position of the heart, the liver and the gas bubble in the stomach indicate the situs of the viscera. In a very few cases, the picture is taken with the back instead of with the front towards the screen. The technicians make a note in such cases. Besides such pictures are easily recognized. The diagnosis has been confirmed by fluoroscopy in most of the cases in which the individual did not know about the anomaly from previous examinations. It can be excluded that any case of normal situs has been taken for a case of situs inversus. However, it can not be excluded that a very few cases have been discarded due to lack of confirmation by fluoroscopy.

In the mass x-ray series were found 2 cases of dextrocardia alone, without other visceral inversions. The frequency of this type of inversion is thus about 0.0001 per cent. Inversion of the abdominal organs alone was observed twice in the 70 additional cases and once in a secondary case, in the twin the brother of whom had situs inversus totalis. Inversion of the abdominal organs alone is probably as rare as inversion of the heart alone.

The occurrence of situs inversus totalis and of inversion of the abdominal organs or metameres of the heart alone in the same family (Torgersen, 1950) indicates that all types of inversion are manifestations of the same factors, the rareness of the partial inversions being partly due to prenatal selection.

Family data. For obvious reasons, a direct examination of all members of the families of such a large series of cases would not have been feasible. In the beginning of the study, I succeeded in examining 60 sibs and parents of a number of cases without encountering additional cases of the anomaly. Earlier studies had, in fact, shown this procedure to be unpromising. Mattison (1933) examined 448 relatives of individuals showing the anomaly, and Gutzeit and Lehmann (1940) performed an extensive examination of the families of 3 cases; in both instances the results were negative.

The best, and in fact the only practicable, way of ascertaining or excluding cases among the sibs and of avoiding selection of data is to examine all of the inhabitants of a limited area having a fairly stationary population. The present

material approaches this goal rather closely. Considering the large numbers of individuals examined, it is highly improbable that cases of situs inversus have been overlooked among the sibs, especially those over 15 years of age. The families have shown much interest in the investigations and have cooperated well in supplying information, probably because situs inversus, unlike other anomalies, is regarded merely as a curiosity rather than a malformation.

It of course cannot be excluded that situs inversus may have passed undetected in some of the parents and sibs. However, the chance of finding additional cases in families has been high. Among the 200 cases found by mass x-ray photography 65 per cent knew of their anomaly from previous examinations, a percentage indicating the relatively high value of hearsay evidence in this condition in Norway at the present time. Internal migration, emigration, prenatal and infant mortality—which is not increased in these families—cannot be considered as sources of serious error.

Through the mass x-ray surveys I found 8 familial cases, among them two cases previously reported (Frøhlich, 1920; Natvig, 1939). Only 25 such families are on record in the world's literature. Affected cases in parent and child have been recorded only twice, in a mother and daughter (Mattison, 1933) and in a father and child of unspecified sex (Pernkopf, 1937). Considering the extensive sampling employed in the present study, which revealed no cases in 2 consecutive generations, such occurrences must be exceedingly rare, even rarer than the cases in sibs.

More emphasis has been placed upon the relation of the data to the population as a whole than to genealogical studies, the results of which are of limited value if the size of the population and conditions of sampling are unknown.

RESULTS

Situs inversus and twinning. The frequencies of situs inversus and twinning in different regions of Norway are shown in table 1. The frequency of situs inversus is lowest in urbanized counties in the East, and highest in the West. The difference between these two groups is 0.013 ± 0.0045 per cent. In a previous report (Torgersen, 1949*a*) the author suggested a possible relation between the geographical distribution of situs inversus and twinning. This preliminary hypothesis, based upon relatively few observations, has since proved to be no doubt erroneous. There is no apparent parallelism between the frequencies of twinning and of situs inversus. As far as the geographical distribution is concerned, the two phenomena seem to behave as manifestations of independent factors.

One reason why a parallelism had been anticipated, both in the geographical distribution and in the familial occurrence, is the fact that both situs inversus and twinning tend to occur in the offspring of older mothers. The average age of the mothers at the time of birth of children with situs inversus is 31.73 years for 227 cases in the present study. On the basis of official Norwegian statistics, E. Sverdrup, of the University Institute of Economics, has calculated that the average maternal age for all births in the interval 1920–30, which is the middle of the period in which the births of the individuals with situs in-

versus in this material took place, is 30.5 years, with a standard deviation of 6 years. The difference, 1.23 ± 0.4 years, shows that maternal age is of importance in situs inversus. However, the influence of this factor is not of such importance as to conceal the independence of the factors in twinning and situs inversus. Unlike twinning, situs inversus is relatively frequent in regions with a high degree of inbreeding.

The data on twinning in the propositi themselves also fail to reveal any significant correlation between situs inversus and twinning. Among 240 unselected cases of the anomaly, 4 were members of twin pairs—about the number to be expected on the basis of chance association. Two of these constituted a pair of dizygotic twins, concordant for situs inversus (Torgersen, 1948*b*). The remaining two cases belong to two different pairs of same-sexed twins; in one case a twin sister had died at one month of age, in the other, a twin sister

TABLE 1. FREQUENCY OF SITUS INVERSUS COMPARED WITH THE TOTAL TWIN FREQUENCY IN VARIOUS PARTS OF NORWAY

REGION	SITUS INVERSUS CASES/TOTAL	SITUS INVERSUS PER CENT	TWINS (§) PER CENT
Districts nearby Oslo Fjord	19/246,602	0.0077	2.76
Eastern and central Norway	22/156,906	0.0140	2.76
Southern Norway	22/161,153	0.0137	2.82
Western Norway	25/120,354	0.0208	2.58
Troendelag (near Trondheim)	20/201,922	0.0099	2.83
Northern Norway	14/111,925	0.0125	2.32
Totals	122/998,862	0.0122	

§ Percentage incidence of twins represents twin-born individuals (counting both partners) relative to total births, according to official Norwegian statistics.

died at age 6 years; there is no conclusive evidence regarding the zygosity of these pairs or about the situs of the viscera in the twins that died.

Data concerning the familial occurrence of twins were secured in 100 unselected families of the index cases. The information regarding twins in the parents and sibs, and possibly also in the grandparents, is probably more reliable than information about twinning in more remote relatives. For this reason, the frequencies of twins in the parents, grandparents and sibs are compared with the frequency in the population. Six of the 200 parents were members of twin pairs, as were 4 of the 400 grandparents. Among the 500 sibs in these families there were 7 pairs of twins. The total of 24 twins among 1,100 individuals is about what is to be expected in a country in which the frequency of twin births is about 1.5 per cent.

How frequently have twins occurred in the families of those cases of situs inversus who were themselves members of twin pairs? In answering this question, the family in which both members of a pair of dizygotic twins showed

situs inversus has to be reckoned twice. Of 16 grandparents, 3 were twins; of 8 parents, none. Two twin pairs were found among 23 sibs. In all, 15 per cent of these 47 relatives were twins. The difference between this frequency and the population incidence is about 13 ± 5 per cent. Thus, the frequency of twinning is probably increased in the very few families in which the individual with situs inversus is a twin.

The number of sibs is known in 229 unselected families, the ratio of affected (situs inversus) sibs to normal sibs being 11:1,221, the 229 index cases being, of course, excluded. In 221 families the index case was the only individual found to be affected. Three sibs were affected in 3 sibships, 2 in 5 sibships; in all, 36 normal sibs were present in these 8 sibships. These data do not agree with the supposition of a single recessive gene. In fact, they can hardly be considered as proof of an influence of the genes at all, environmental factors not being excluded.

On the other hand, evidence for the hereditary nature of situs inversus is available from other observations. There is first the genetical relationship with other anomalies, as demonstrated by the author in connection with developmental anomalies of the lungs and heart (Torgersen, 1946, 1949*a*, *b* and 1950). Situs inversus behaves in these families as a manifestation of genes which, in the previous generation or in the sibs, show quite different manifestations. Additional evidence of heredity is furnished by the frequency of consanguineous marriages among the parents of situs inversus cases, and particularly of first cousin marriages, which, in 189 unselected cases, was found to be 3.7 per cent.

A more detailed analysis shows that the parents were second cousins twice in the 8 familial cases, first cousins in none of them. It is remarkable that no secondary case occurs among 48 sibs of 7 sibships in which the parents were first cousins. But in 44 families having symptoms of a defective development of the bronchi and the paranasal sinuses, the patient with situs inversus had parents who were first cousins in 3 cases (7 per cent) and second cousins in 7 cases (16 per cent), in contrast to 2.2 per cent first cousin marriages and 3.8 per cent second cousin marriages in the other families. This varying frequency of parental consanguinity for different groups of cases of situs inversus is in accord with the assumption of several genes, the number of factors and their relative importance varying from group to group. The genes causing bronchiectasis and nasal polyps show incomplete dominance. The probability of their manifestation increases with the probability of visceral inversion, which in turn is increased by homozygosity for certain genes influencing the asymmetry of the viscera.

The parents were not related in any of the cases in which the individual with situs inversus was a twin. One of the twin cases was a woman who had severe symptoms of bronchiectasis and nasal polyps, her father also had shown the same symptoms. In one case of situs inversus, the mother was a twin and was a first cousin of the father. In another case, the father was a twin and two of his children (including the propositus) showed situs inversus, one of them (the propositus) having bronchiectasis as well. In another family, the male propositus, an only child, showed situs inversus and congenital heart disease; twin births occurred as a probable hereditary trait in his father's family, and congenital heart disease occurred in the family of his mother.

Situs inversus and left-handedness. As the question of left-handedness looms prominently in the literature both on twinning and on situs inversus, a summary of the data concerning handedness in the present material may also be of interest. My observations confirm the statement of Cockayne (1938) that the incidence of left-handedness is not increased in situs inversus. Among 160 unselected individuals with the anomaly 11, or 6.9 per cent, were left-handed; among 715 of their sibs 25, or 3.5 per cent, were left-handed; and among 320 parents 17, or 5.3 per cent, were left-handed. The differences can be explained by the fact that information about handedness was obtained from the individual with situs inversus. The data do not, of course, indicate the absolute frequency of left-handedness in the material; they serve merely as an indicator of the relative frequencies of left-handedness in the groups compared. They cannot be fairly compared with material from other countries nor with surveys conducted in other ways. However, in passing, we may note that Mattison (1933) found left-handedness in 3.4 per cent of 448 relatives of his situs inversus cases.

The present observations on single-born subjects with situs inversus agree in general with the findings of Verschuer (1933), who stressed the independent nature of particular asymmetries observed by him in twins. Verschuer considered this as evidence that a mirror-image mechanism is of little importance in producing symmetry reversals in twins.

Both parents were left-handed in two of the cases contained in the present series of situs inversus cases; in these sibships 2 out of 16 sibs were left-handed. In one family, 3 children and the mother were left-handed; the child with situs inversus suffered from bronchiectasis, and a sib from nasal polyps. The father, who was right-handed, had 7 sibs all of whom were said to be left-handed. These observations offer no proof of a genetic relationship between situs inversus and left-handedness, however, since coincidental occurrence of hereditary factors for the two conditions would be expected in a few families in survey that comprises a large fraction of the total population.

Left-handedness was found among 13 $\pm$ 3 per cent of 131 children in families having one or both parents left-handed, and in 3 $\pm$ 0.6 per cent of 980 children of right-handed parents. Previously, Rife (1940) found, among children resulting from these same two mating categories, 40 out of 145 and 151 out of 1842 left-handers, respectively. The data so far indicate that genes showing incomplete dominance are of importance both in left-handedness and in situs inversus.

DISCUSSION

In the case-history literature, situs inversus has been observed in 12 pairs of probable MZ twins, 6 times concordantly and 6 times discordantly (Reinhardt, 1912; Cockayne, 1938; Gänslen *et al.*, 1940; Werner, 1940; Kean, 1942;

Helweg-Larsen, 1947). In Reinhardt's case of concordant MZ twins, the parents were first cousins and the mother was one of twins. In the discordant pair of male twins described by Helweg-Larsen, the unaffected twin produced one single-born child and a pair of twins that miscarried in the third month of pregnancy.

Only three cases of DZ twins with situs inversus are recorded. One of these is a concordant pair described by the author (Torgersen, 1948*b*). Doolittle (1907) observed dextrocardia in a man who had a twin sister; both of his parents were members of twin pairs, and he himself produced opposite-sexed twins, the boy again showing dextrocardia.

As already emphasized, such case-history observations are of limited value because the sizes of the populations from which they have been drawn are unknown. They no doubt merely parallel the coincidental cases observed in the present population study. At any rate, they can hardly be considered as providing crucial evidence either for the existence of genetic factors in situs inversus or for a relationship between visceral inversion and twinning. The concordant MZ cases might be due to prenatal environmental factors acting similarly on both twins. On the other hand, the discordant MZ cases do not prove the operation of a difference-producing mirror-image mechanism; the responsible prenatal environmental factors may be supposed to act only on one of the twins, or the hereditary factors may be expressed in only one of them. The occurrence of concordant DZ twins suggest an influence of hereditary or environmental factors acting on both twins. As to the relative scarcity of reported cases of situs inversus in DZ twins, this might be attributable merely to a preferential recording of MZ pairs, or it might conceivably indicate a high prenatal mortality in such pregnancies.

The simplest interpretation of the relatively high frequency of twins in the families in which the propositus with situs inversus is one of twins is to assume a coincidental occurrence of genetical factors for twinning and for visceral inversion in these families.

The hereditary mechanism in situs inversus is still far from being cleared up. The importance of the genes is evident, however. The genetic behavior shows some striking similarities to the interpretations of Landauer concerning the inheritance of asymmetrical expression of genes in the domestic fowl (Landauer, 1948; Torgersen, 1949*a*).

Rife (1940) observed a high frequency of left-handedness among relatives of twins showing intrapair difference in handedness, as contrasted with a low frequency of left-handed relatives of twins where both were right-handed. The comparison with the present findings on situs inversus and associated anomalies is striking. The evidence so far suggests similar but independent hereditary mechanisms in situs inversus and left-handedness, and a parallelism in the relations of both kinds of asymmetry to twinning.

The frequency of left-handedness in twins is controversial. Dahlberg (1926) and Newman (1937) are of the opinion that left-handedness is relatively frequent in one of a pair of MZ twins. Siemens (1924) and Newman also found an increased frequency in dizygotic twins; whereas Schiller (1937) concludes that left-handedness is not particularly frequent in either type.

If left-handedness and twinning, in the same way as situs inversus and twinning, depend upon independent genetic factors, one would expect these genes to occur with the same frequency in zygotes giving rise to MZ twins or to single-born individuals. However, the factors may be supposed to have a greater chance of manifestation in two individuals with this genotype than in one individual. For this reason, one has to expect a relatively high frequency of left-handedness in MZ twins. Dahlberg found among 124 pairs: 6 pairs both left-handed, 29 pairs with one left-handed, and 89 pairs both right-handed. Here again, as in situs inversus, it is not necessary to suppose a mirror-image mechanism to account for these asymmetry reversals, nor is there reason to suppose any particular relation to twinning.

Similarly, one would expect to find concordancy for left-handedness or situs inversus relatively frequently in DZ twins, since both are genetically determined. Schiller found among 125 pairs: 1 pair both left-handed, 32 pairs with one left-handed, and 92 pairs both right-handed. The single concordant left-handed pair parallels the single DZ pair concordant for situs inversus in the present material. On non-genetic chance concurrence, the probability of situs inversus in both members of a DZ twin pair would be exceedingly small. However, the probability of finding situs inversus in a full sib of an index case is about 1 in 100, judging from the present study, so concordance in DZ twins would occasionally be expected (Torgersen, 1949*a*).

It is hardly possible at present to estimate the relative influence of hereditary and prenatal environmental factors in the causation of situs inversus and handedness, either as manifested in single-born individuals or in MZ twins. The observations so far indicate that modifiers influencing bilateral differentiation play an important part in these asymmetries. They confirm the suggestion of Dahlberg (1926) that there are genotypically controlled asymmetries not only in the single-born, but also in MZ twins. Probably the fundamental effect of these modifying genes concerns the reactive potency of the embryonic field in which particular genes take effect, as proposed by Laundauer in connection with certain asymmetrically expressed abnormalities in the domestic fowl. The reactive potency of the human egg is apparently relatively strongly determined by these modifying genes, so that the mirror-image mechanism, known from experimental work on amphibian twins, is of relatively little importance in human MZ twins. This greater regulatory power of the human egg tends to allow regeneration of the two halves of the embryo to equipotential systems from the point of view of experimental embryology. Thus, the developmental potentialities are apparently determined mainly by the genes and by genetically determined bilateral differentiation at the time of division. The data of the present study do not, of course, exclude the existence of asymmetries in twins due to incomplete regulation. They do, however, suggest that

the mirror-image mechanism is of relatively little importance compared with the genes influencing visceral asymmetry and handedness.

SUMMARY

The present report is based upon 270 cases of situs inversus, most of which were discovered in mass roentgenographic surveys of the Norwegian population. It is estimated that the entire country contains about 340 cases of the anomaly, or an incidence of 0.011 per cent. Geographically, the varying frequencies of situs inversus do not parallel the total twin birth frequencies in different regions of Norway.

Among 100 unselected cases of situs inversus and their sibs and parents neither twinning or left-handedness was observed with frequencies greater than those expected on the basis of chance association. The evidence thus far indicates that visceral inversion and left-handedness are fundamental asymmetries due to similar-acting but independent hereditary factors having no particular relation to the factors in twinning. The data further suggest that the developmental potentialities for bilateral differentiation of the human egg are so strongly determined genetically that the mirror-image mechanism, as revealed in experimentally produced amphibian twins, is of relatively little importance in human polyembryony.

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Congenital Malignant Neuroblastoma of the Suprarenal Gland in One of Twin Girls

HENRY BRODY[1]

Department of Laboratories, Beth Israel Hospital, New York 3, N. Y.

H. G. WELLS (1940), in his collective review of congenital malignant neoplasms, listed four cases as "actually or at least possibly malignant neoplasm" in twins. I have not found any additional cases in a review of the literature since that date. In reviewing some material from the files of this hospital, an old case of definitely malignant and congenital neoplasm in one of twins was found, and it was thought that the case should be placed on record.

Twin girls were born to a young woman, her first pregnancy. One infant had a distended abdomen, which was interpreted to be a large liver. She died on the fourth day of life. Autopsy revealed a tumor of the medulla of the left suprarenal gland, with massive metastases to the liver (figs. 1–3). Microscopic study showed a sympathoblastoma, with involvement of the medulla of the right suprarenal and metastases in spleen, lymph nodes and bone marrow of a rib, in addition to the massive destruction of the liver (figs. 4–7). Sections of vertebrae, brain, lungs, heart, kidneys, pancreas, thymus, thyroid, tongue, esophagus, larynx, fallopian tube and ovary showed no tumor. The heart showed no congenital anomaly.

Unfortunately, there are no notes in the charts of either the mother or the babies which would indicate that the placenta had been carefully studied to ascertain if the twins were monochorial; the blood types of the babies were not determined, and anthropometric studies were not carried out. The mother's hospital chart bears the numerical index notation indicating "twin pregnancy, uniovular", but at the present time it is not possible to ascertain on what basis it was so coded. The twin sister is known to be alive, and presumably free of tumor, at the present writing, fourteen years later. She has a congenital heart lesion, of the cyanotic type, for which she has been under the care of a pediatrician. The mother has had one subsequent pregnancy, with delivery of a normal child.

Macklin (1941) has reported 109 pairs of twins with tumors, not all malignant, and some of questionable authenticity. There have been additional reports since. No cases, other than those listed by Wells, have been definitely congenital. Possibly congenital are case 2 of Macklin, and the cases reported by Benedict (1929), Duncan and Maynard (1939), and Falls (1947), all being cases of retinoblastoma, which notoriously is a congenital tumor.

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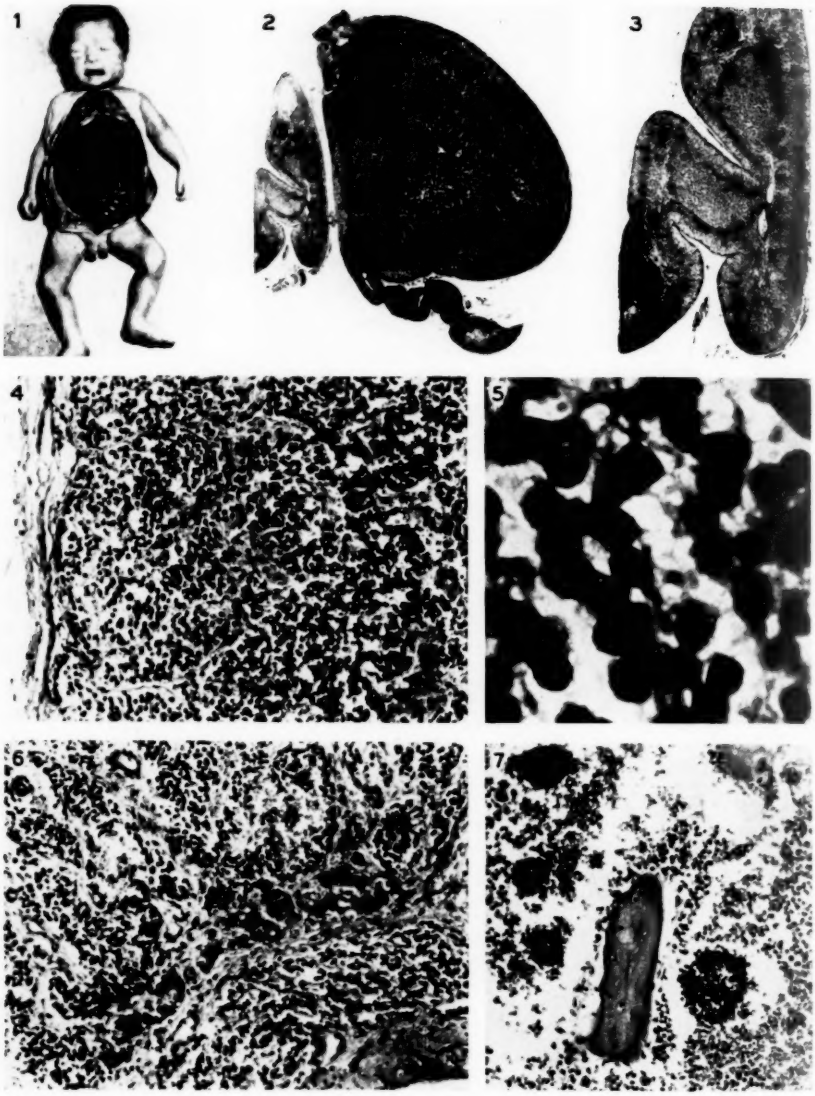
[1] Present address: Jewish Hospital, Philadelphia 41, Pennsylvania.



FIGS. 1–7

It is of interest that in none of the cases of congenital and definitely malignant tumors—all neuroblastomas—of the adrenal (Amberg, 1904; Rostkowski, 1932; this report) was there evidence of involvement of the co-twin, though only in the present case is the fate of the second twin certainly known. Unfortunately, in none of these cases was there any study of the placenta. The hematogenous spread of the tumor is clearly demonstrated in the present case; metastasis to the placenta may have occurred. If the twins were truly monozygous, and if they also had a common placental circulation, metastasis to the second twin would have been possible. It did not occur. Nor did transplacental metastasis to the mother become manifest. Metastasis from fetus to mother has never been described, to my knowledge.

Wells concluded that, except for the retinoblastoma, "tumors that tend to be congenital or to appear early in infancy show no apparent familial or hereditary influence." The absence of involvement of the co-twins in the five cases of congenital tumor in twins is in agreement.

SUMMARY

A case of congenital, malignant, metastasizing neuroblastoma of the suprarenal gland in one of reportedly uniovular twin girls is described. This is the third case of congenital neuroblastoma in one of twins to be reported.

Acknowledgements: I should like to thank Dr. E. Diamond and Dr. H. Douglas for the clinical report, particularly as to the current status of the living twin; and Mr. Julius Weber for the microphotographs.

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FIG. 1. Abdominal situs, showing massive metastases in liver.

FIG. 2. Right and left adrenals in longitudinal section, showing the large medullary tumor in the left, and the microscopic foci (dark areas) in the right. 3 ×

FIG. 3. Microscopic foci of tumor in right adrenal medulla. 8 ×

FIG. 4. Tumor invading cortex, left suprarenal. 100 ×

FIG. 5. High power, showing cellular detail. Note tendency toward rosette formation. 400 ×

FIG. 6. Destruction of liver by tumor. Note bile duct in lower right corner, and upper left; preserved liver cords are seen running diagonally below center on the right. 100 ×

FIG. 7. Metastatic foci in marrow of rib. 100 ×

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Discordant Monozygotic Twins with Retinoblastoma and Cleft Palate

NORMA FORD WALKER

Department of Zoology, University of Toronto, Toronto 5, Ontario, Canada

THE present paper contains a description of monozygotic twins showing discordance for two inherited anomalies, namely, retinoblastoma and cleft palate. There is also appended a report of trizygotic triplets, one of whom was affected with retinoblastoma.

So far as we can ascertain there are at least 3 published accounts of retinoblastoma in one-egg twins. Benedict (1929) reports concordance for twin girls, aged $4\frac{1}{2}$ years, one of whom had a tumor in the left eye and the other a tumor in each eye. Duncan and Maynard (1939) report a case of Italian twins in Australia, describing this case as one of "identical tumors in identical twins," but they present no evidence to show that the infants were monozygotic. There was a bilateral involvement in each twin. Falls (1947) describes monozygotic twin girls, each with bilateral retinoblastoma. Moore and Scott (1929) report discordance for twin girls, aged 2 years, one of whom had a bilateral involvement, but the authors give no indication as to whether these twins are monozygotic or dizygotic.

Many pedigrees have been published in which more than one sib is affected with retinoblastoma or in which two generations are affected (Falls, 1946). There is one pedigree extending into three generations (Griffith & Sorsby, 1944) and possibly into four (Weller, 1941). The majority of cases, however, appear to be sporadic, and Haldane (1949) has calculated the rate of mutation per generation as 1.4×10^{-5}. The disease is believed to be inherited as a dominant, but Cotterman (1950) points out that if one attempts to explain the whole disease in terms of a single dominant gene, there are facts demanding the assumption of incomplete penetrance, something less than 100 per cent, but probably not less than 50 per cent.

In all studies of retinoblastoma it should be borne in mind that the diagnosis can be made with certainty only after enucleation, when histological sections of the eye have been examined. A differential diagnosis can then be made with pseudoglioma (Wilson, 1949) and retrolental fibroplasia (Owens & Owens, 1949). The term "retinoblastoma" was adopted about 1925 by the American Ophthalmological Society in place of "glioma of the retina."

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Isolated cleft palate according to Fogh-Andersen (1942) has no genetic connection with harelip with or without associated cleft palate. Isolated cleft palate occurs more frequently in females, the manner of inheritance being that of simple dominance with the degree of manifestation probably considerably below 50 per cent. Among 9 pairs of monozygotic twins Fogh-Andersen found only 1 concordant pair with isolated cleft palate.

It may be that in some instances either retinoblastoma or cleft palate is non-hereditary, arising as a result of unfavorable environmental factors.

DISCORDANT MONOZYGOTIC TWINS WITH RETINOBLASTOMA

The present case concerns twins, Florence and Evelyn A., born August 21, 1932 in Indiana. They were first studied genetically at the Hospital for Sick Children, Toronto, in 1942, when the author and Miss Grace Giles were surveying cases of harelip and cleft palate. Recently the case has been reviewed again, the girls being now 18 years of age and in good health.

Florence was admitted to the Hospital for Sick Children at 8 years of age for a Dorrance pushback operation of the soft palate, performed by Dr. A. B. LeMesurier, and as a result the child's speech was improved. At 2 years of age she had had repair operations at the Methodist Hospital, Gary, Indiana. The cleft in the palate had apparently extended forward at least as far as the alveolus. Her twin, Evelyn, shows no evidence of cleft palate, but at 2 years of age had her left eye removed in the Methodist Hospital by Dr. C. Boardman because of retinoblastoma. Several physicians agreed upon the diagnosis, including Dr. H. A. Kuhn and Dr. Robert Von der Heydt, from whom we have statements advising enucleation. A histological report from Dr. H. M. Banks of the Methodist Episcopal Hospital of Indianapolis is as follows: "Histological section thru the globe of the eye, shows a tumor-like mass of neoplastic cells, springing from the retinal coat, piling up into very irregular arrangement of cells, quite easily identified as being derived from the retinal layer. These structures are quite massively formed, seemingly in cluster-like arrangement around the blood vessels which supply the tumor mass. The blood vessels are quite rudimentary and undifferentiated in general cellular composition. The cells that compose these mantles are quite irregular in size and shape, nuclear structures are quite bizarre in arrangement, and loose and lace-like; atypical mitoses are abundant. *Impression:* Glioma of the eye. There was no evidence of penetration of any portion of eye by tumor, nor evidence of penetration of optic nerve at any point beyond level of choroid coat." Follow-up studies have failed to show evidence of the tumor in the remaining eye of Evelyn or in the two eyes of Florence.

Family History

No previous occurrence of either retinoblastoma or cleft palate is recorded within the family. The family is Scottish and gave a clear and detailed pedigree.

It is of interest that Mr. A's paternal grandfather (born in 1815) was an identical twin. Mr. A. recalls that these twins lived to be over 80 years old and the only way in which he could tell his grandfather from the twin-brother was by his grandfather's "blind eye," which Mr. A. understood had been injured in a mine explosion, although at what age Mr. A. did not know. Mrs. A. was the second youngest of a family of 10 children. She died of a cerebral hemorrhage in Toronto in the interval between the two interviews. Mr. A. was a first-born, with 4 sibs and 5 step-sibs, his father having married twice. The twins, Florence and Evelyn, have 18 paternal first-cousins. So far as we could ascertain, there was no history of other malignancy in the family.

Birth Records

The twins were born at a second pregnancy on August 21, 1932, when their mother was 33 years old, their father 34 years. Their only sib, a sister, is 6 years older, and, although no miscarriages occurred during that interval of six years, the mother reported that at the third month of her twin pregnancy she passed "a clot, the size of a small egg" which she assumed was a blood clot. The obstetrician feared a termination of pregnancy.

Evelyn was the first born. The birth weights, as recalled by the father, were: Evelyn, 4 lbs. 11 oz.; Florence, 2 lbs. 11 oz. It is also stated that they were full term infants. Florence was kept in an incubator for a month.

Unfortunately, there are no records available regarding the birth membranes or placental structures.

Zygosity of the Twins

Although the main determination of the zygosity of the twins was based upon the analysis of the dermal configurations, other physical characters were also taken into consideration. As can be seen from figure 1 there is so close a resemblance between the twins that they are constantly mistaken for each other. The general similarity is borne out in detailed comparisons of hair color and form, skin tones and distribution of freckles, ear shape and proportions, as well as in the form of the mouth and nose. In height and weight the twins show close agreement. Evelyn had an early tendency to be left-handed, but this was easily corrected.

The eye color of both twins is blue with a slight trace of brown pigment around the pupil (S9, Saller chart), but with this difference that the lighter areas in the iris of Evelyn's right eye were chalkier, giving more of a pepper and salt pattern than is seen in Florence's eyes. This observation may have some significance as an indication of disturbed fetal growth, since a "speckled iris" in mongoloid imbeciles occurs with high frequency (Lowe, 1949). In mongoloids these speckled areas can be seen most readily shortly after birth. Later if the eye takes on brown pigmentation, the chalky areas are obscured but will continue to show in blue eyes.

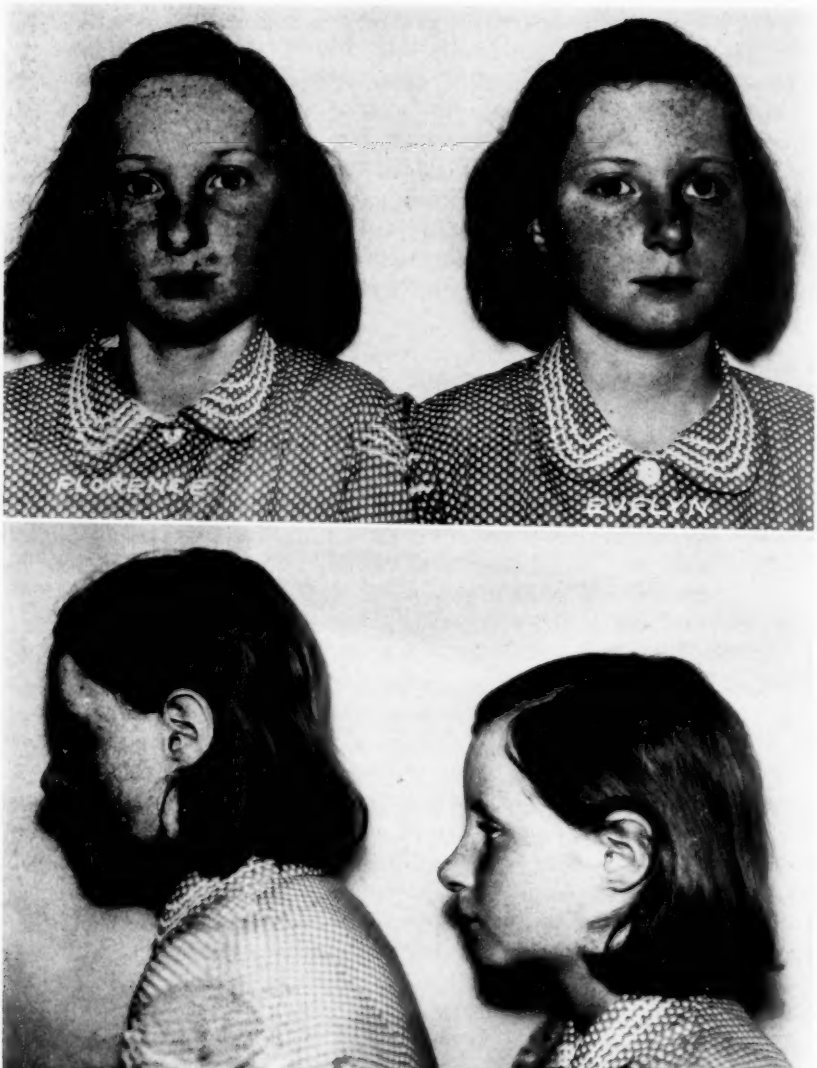

FIG. 1. Photographs of monozygotic twins, Florence (*left*) and Evelyn A. (*right*), at age 10 years, showing their marked physical resemblance, including the distribution of freckles. The left eye of Evelyn was enucleated for retinoblastoma at 2 years of age. In profile photographs the twins are sitting at different heights.

The eye color of other members of the family were variations of blue or hazel: Mrs. A., hazel, M 8; Jean, blue, S 8 around the pupil, S 10 at the margin of the iris; Mr. A., left eye blue, S 8; right eye one-quarter brown medianly, the rest blue, S 8 (heterochromia iridis).

The blood group of the twins and their father is Group B. A comparison of the blood groups and other physical features supports a diagnosis of monozygosity.

TABLE 1. DIGITAL PATTERNS AND RIDGE COUNTS FOR THE TWINS (FLORENCE AND EVELYN A.), THEIR PARENTS AND SIB

NAME	LEFT FINGERS					RIDGE COUNTS	RIGHT FINGERS				
	5	4	3	2	1	L R Total	1	2	3	4	5
Florence	U 0-3	U 0-9	U 0-12	U 0-11	U 0-9	44 53 97	U 13-0	U 17-0	U 13-0	U 6-0	U 4-0
Evelyn	U 0-5	U 0-11	U 0-6	U 0-9	U 0-11	42 57 99	U 18-0	U 15-0	U 9-0	R 0-8	U 7-0
Mr. A.	U 0-11	U 0-12	U 0-9	U 0-6	U 0-11	49 48 97	U 17-0	U 11-0	U *6-0	W 3-2*	U 11-0
Mrs. A.	U 0-11	W 9-19	U 0-19	U 0-15	W 6-5	70 86 156	W 13-10	W 19-14	U 15-0	W 22-15	U 17-0
Jean	U 0-14	W 17-19	W 15-16	U 0-13	W 5-6	68 80 148	W 16-1	U 15-0	U 18-0	W 17-17	W 14-5

Symbols: U, loop ulnar; R, loop radial; W, whorl.
* Fingers scarred, counts approximate.

Dermal Configurations

Dermal prints of the twins, their parents and sister were made by the Faurot method and formulated according to standard methods (Cummins & Midlo, 1943). The digital patterns and ridge counts are summarized in table 1, the palmar formulae in table 2 and the plantar in table 3. The homolateral differences in the digital and palmar configurations of the twins, their parents and sib are brought together in table 4. The homolateral differences in the plantar configurations of the twins alone are shown in table 5.

From table 4 it is seen that the average difference between the twins is 6.3, which value agrees with that for monozygotic twins (15.9) rather than with dizygotic (34.0). It is also seen that the twins bear a closer relation to their father in their digital and palmar patterns than they do to their mother

or sib. From table 5 it is found that the differences for plantar configurations (42.5 and 45.0) agree more closely with the averages for monozygotic twins (32.1 and 32.7) than for dizygotic twins (66.0 and 62.5).

From the above analysis it is concluded that Florence and Evelyn are monozygotic twins.

TABLE 2. PALMAR FORMULAE OF THE TWINS (FLORENCE AND EVELYN A.), THEIR PARENTS AND SIB

NAME	LINEAR FORMULA D . C . B . A	AXIAL TRIRADII	HYPO . T/I_1 . I_2 . I_3 . I_4
	Left Palms:		
Florence	7 · 5″ · 5″ · 1	– t′(33.3) –	A^u/A^e · O · O · O(V) · L
Evelyn	7(8) · 5″(6) · 5″ · 5′	– t′(33.3) –	A^u(V)/A^e · O · O · O(V) · L
Mr. A.	7(8) · 5″(6) · 5″ · 5′	– t′(17.4) –	A^u/A^e · O · O · O(V) · L
Mrs. A.	11(10) · 9 · 7(6) · 4(5)′	– t′(30.0) –	A^u/A^e · O · O · l · V(O)
Jean	9(10) · 7 · 5″(6) · 4(5)′	– t′(23.1) –	A^u/A^e · O · O · O · l
	Right Palms:		
Florence	7(8) · 5″(6) · 5″ · 5′	– t′(33.1) –	A^u/A^e · O · O · O · L
Evelyn	7(8) · 5″(6) · 5″ · 5′	– t′(34.4) –	A^u/A^e · O · O · O(V) · L
Mr. A.	9(8) · 7(6) · 5″ · 5′	– t′(16.5) –	A^u/A^e · O · O · O(V) · L
Mrs. A.	11(10) · 0 · 7(6) · 5′(4)	– t′(25.3) –	A^u/A^e · O · O · O · O
Jean	10 · 9 · 7(6) · 5′	– t′(29.4) –	A^u/A^e · O · O · l · O(V)

Symbols: A^u, arch ulnar; A^e, arch carpal; L, large loop; l, small loop; O, open field; V, vestigial; Hypo., hypothenar; T/I_1, thenar and first interdigital; I_2, second interdigital; etc.

TABLE 3. PLANTAR FORMULAE OF THE TWINS, FLORENCE AND EVELYN A

NAME	LINEAR FORMULA D . C . B . A	PATTERN FORMULA . Hal . Hypo. Cal . Then(1). Then(2) I_1 . I_2 . I_3 . I_4
	Left Soles:	
Florence	15 · 9 · 9 · 15(7)	· 13 · L^t · O · O · O/L^d · L^{pd}y · l^d/L^dy · O
Evelyn	15 · 9I · 7 · 7	· 13 · L^t · O · O · O/L^dy · L^{pd} · W · O
	Right Soles:	
Florence	15(13) · 9 · 7 · 0	· 13 · L^t · O · O · O/L^dy · O · L^d · O
Evelyn	15 · 9I/10 · 8 · 7	· 13 · L^t · O · O · O/L^dy · L^{pd} · W · O

Symbols: L^d, loop distal; L^{pd}, loop proximal turning distally; W, whorl; y, proximal triradius; 9 I, main line directed towards 9, but terminating within an interdigital pattern; underline bar (————) indicates fusion of digits.

Comments on Disturbed Fetal Growth

Differences in the digital and plantar configurations of the twins, Florence and Evelyn, offer some points worthy of comment. The digital patterns of Florence are 10 ulnar loops; those of Evelyn, 9 ulnar loops and a radial loop on the fourth right digit. It has already been determined by the author in connection with studies of mongoloid imbeciles that the most frequent digital combination for these defectives (in whom there is a marked disturbance of

fetal growth) is 10 ulnar loops. Among 151 mongoloids (70♂♂, 81♀♀) approximately 38 per cent showed this distribution, while in a control group of 500 (252♂♂, 248♀♀) only 12 per cent did so. A comparison of the percentage frequencies of the digital patterns in mongoloids and normals is shown in table 6. We assume therefore that there is some association between the types of patterns and disturbed fetal growth.

TABLE 4. HOMOLATERAL DIFFERENCES IN THE DIGITAL PATTERNS AND RIDGE COUNTS, MAIN LINES AND PALMAR PATTERNS OF THE TWINS (FLORENCE AND EVELYN A.), THEIR PARENTS AND SIB

SETS COMPARED	DIGITAL PATTERNS	RIDGE COUNTS	MAIN LINES & AXIAL TRIRADII	PALMAR PATTERNS	AVERAGE
Monozygotic Twins (53 pairs Walker, 1950)	23.0 ± 1.4	10.9 ± 1.0	17.6 ± 1.4	21.4 ± 1.8	15.9 ± 0.9
Dizygotic Twins (20 pairs Walker, 1950)	47.0 ± 4.4	32.5 ± 4.5	31.5 ± 2.2	32.0 ± 8.9	34.0 ± 2.2
Florence					
— Evelyn	10.0	4.8	10.3	0.0	6.3
— father	10.0	8.0	26.5	0.0	11.1
— mother	50.0	47.2	62.2	25.0	46.1
— sib	60.0	40.8	45.3	20.0	41.5
Evelyn					
— father	10.0	12.8	16.8	0.0	9.9
— mother	50.0	45.6	52.5	25.0	43.3
— sib	60.0	39.2	35.5	20.0	38.7

TABLE 5. HOMOLATERAL DIFFERENCES IN THE MAIN LINES AND PLANTAR PATTERNS OF THE TWINS, FLORENCE AND EVELYN A., COMPARED WITH THE AVERAGE DIFFERENCES FOR TWINS

SETS COMPARED	MAIN LINES	PLANTAR PATTERNS
Florence & Evelyn	42.5	45.0
Monozygotic Twins (51 pairs Walker, 1950)	32.1 ± 2.7	32.7 ± 2.2
Dizygotic Twins (20 pairs Walker, 1950)	66.0 ± 8.9	62.5 ± 4.6

In table 6 it will also be noted that the occurrence of a radial loop on the fourth right digit has a frequency of 5.7 per cent in mongols, 0.3 per cent in the control group. The presence of this pattern in Evelyn suggests a somewhat greater disturbance of fetal growth than that experienced by her identical twin.

In the fetal development of the feet, Evelyn's plantar configurations record a partial fusion of digits II, III and IV of the left foot, while Florence's show no such fusion (Fig. 2). This is taken as another indication of disturbed growth. Since dermal configurations are established during the third and fourth months,

it may be argued that at that time Evelyn's fetal growth underwent a disturbance not shared by her identical twin.

TABLE 6. COMPARISON OF PERCENTAGE FREQUENCIES OF DIGITAL PATTERNS IN MONGOLOIDS AND CONTROL

(Percentages for mongoloids based on the finger patterns of 177 imbeciles, for the control on 328 individuals)

Left Digits

PATTERN	V		IV		III		II		I	
	Mongol	Control	M.	C.	M.	C.	M.	C.	M.	C.
W	18.3	12.0	32.8	35.9	13.6	17.4	11.9	33.4	22.4	30.8
U	77.1	85.4	58.7	60.2	83.5	71.4	82.4	36.3	73.0	62.7
R	2.9	0.0	5.1	0.9	1.7	2.6	2.3	19.4	0.6	0.8
A	1.7	2.6	3.4	3.0	1.1	8.6	3.4	10.9	4.0	5.8

Right Digits

PATTERN	I		II		III		IV		V	
	Mongol	Control	M.	C.	M.	C.	M.	C.	M.	C.
W	25.9	38.6	14.9	35.7	11.3	19.4	31.8	46.6	18.9	14.6
U	70.6	57.3	82.3	31.1	86.4	70.9	60.2	52.0	75.4	84.0
R	0.0	0.8	1.7	20.3	1.1	3.4	5.7	0.3	4.6	0.3
A	3.5	3.3	1.1	12.9	1.1	6.3	2.3	1.1	1.1	1.1

Symbols: W, whorl; U, loop ulnar; R, loop radial; A, arch.

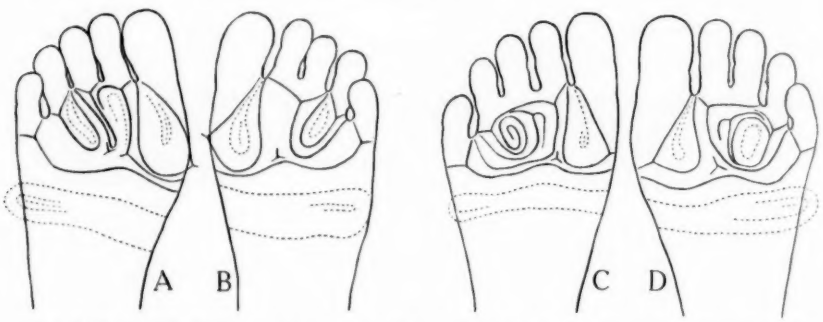

FIG. 2. Outlines of plantar configurations of monozygotic twins. A, left sole of Florence; B, right sole of Florence; C, left sole of Evelyn; D, right sole of Evelyn.

DISCORDANT TRIZYGOTIC TRIPLETS WITH RETINOBLASTOMA

Of 18 proven cases of retinoblastoma admitted over the past 29 years to the Hospital for Sick Children, Toronto, two boys were sibs and one boy was a triplet. Diagnoses of these cases were reviewed recently by Dr. C. L. Rodgers. Briefly summarized the cases are as follows:

	Total cases	*Left eye*	*Right eye*	*Bilateral*
Males	9	3	5	1
Females	9	6	1	2

The triplet was one of a set consisting of a girl and two boys, born November 21 and 22, 1936, in the Soldiers' Memorial Hospital, Orillia, Ontario. Their birth was attended by Dr. W. E. Brown and the infants were cared for postnatally in this hospital for four months, since the parents lived some 10 miles out in the country. The mother, a primipara, was 22 years of age. Later she had three single births, a son and two daughters. The obstetrician, the surgeon (Dr. J. C. Hill) and the mother are all of the opinion that the two boys in the set of triplets were easily distinguished from each other and hence the set was derived from three ova (trizygotic).

The weights of the triplets at birth and when discharged from hospital on March 28, 1937, were:

Anne, 4- 7¼ to 10-7¾ pounds
Beverley, 4-10½ to 10-5 pounds
Christopher, 4- 6 to 10-8 pounds

On January 16, 1938, at 14 months of age, Christopher was admitted to the Hospital for Sick Children, where a diagnosis of retinoblastoma was made by Dr. Lloyd Morgan and enucleation of his left eye was advised. This was performed on January 29, 1938 by Dr. J. C. Hill at the Soldiers' Memorial Hospital in Orillia. On February 18 and March 6, 1938, the child had mastoidectomies and died March 12, 1938.

The histological report received from H. A. Ansley of the Division of Pathology of the Ontario Department of Health reads as follows:

"The specimen consists of an eye 2 cm. in diameter. The iris is irregular and the pupil shows a yellowish discolouration. The anterior chamber is slightly increased in thickness, the iris shows no adhesions. The retina shows umbrella detachment. Apparently arising from the margin of the ciliary body is an irregular mass protruding into the posterior chamber shading into a yellowish opacity of the vitreous. The lens is transparent but of a bright yellow colour.

"*Microscopic Report:* Section through the eye shows the retina detached and uniformly thickened by proliferation of cells which closely resemble retinal tissue, but show large areas of tumor necrosis. In some areas the cells appear to be round cells, while in others they possess definite fibrils and in some areas also are seen to form rosettes. The general appearance and arrangement of the tumor is that of a diffuse cancerous proliferation of the retina rather than a localized tumour growth. No extension is seen into the optic nerve, however. *Diagnosis:* Retinoblastoma."

Family History. The mother of the triplets was one of 6 children, there being 4 younger sisters and one brother. These sibs have now 8 daughters and 7 sons. The mother had maternal twin uncles, believed to be binovular. The father of the triplets was the youngest in his family, having 3 brothers and 3 sisters, 5 nephews and one niece. Throughout the paternal and maternal relatives there is no known history of retinoblastoma. The father has an enucleated left eye but there is documentary evidence from the Peterborough Civic Hospital to show that this was due to a railway accident which occurred on July 12, 1927, when the father (aged 24 years) was hit by flying steel. The steel was removed with a magnet, and some of the iris tissue was excised. By September 28, 1927, iridocyclitis had developed and the eye was enucleated.

SUMMARY

1. Two cases of retinoblastoma in multiple sets are described, the diagnosis being established in each case by histological reports.

2. One case concerns twins whose monozygosity was determined through an analysis of dermal configurations and other physical characters.

3. The monozygotic twins show discordance for both retinoblastoma and cleft palate, one twin showing uniocular retinoblastoma, the other cleft palate.

4. It is suggested that disturbance of fetal growth at the third and fourth fetal months (as recorded by the dermal configurations) is more marked in the twin affected with retinoblastoma.

5. The second case concerns a set of trizygotic triplets, one member of whom was affected with retinoblastoma of the left eye.

6. No family history of the anomalies described was elucidated in either case.

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The Genetics of Psychoses

An Analysis of 1,232 Twin Index Families[1]

FRANZ J. KALLMANN

Department of Medical Genetics of the New York State Psychiatric Institute, Columbia University, New York 32, N. Y.

If there are some colleagues among the European members of the Congress, who are familiar with the history, volume and general objectives of our research in psychiatric genetics and social psychiatry during the past 25 years, they will need no descriptive account of my own disappointment caused by the inability to open the panel discussions of the Section of Social Psychiatry with a personal report on the recent progress of our work. With respect to those others who know little about me, I prefer to limit this introductory comment to expressing not only my appreciation of having been invited to participate as a panel speaker in the proceedings of this Section, but also my regret at the circumstances which prevented my presence at this long-planned event. I definitely hope, however, that the printed record of our long-term studies, although highly condensed and still incomplete in various respects, will somehow suffice to speak for itself.

As regards the scientific background of my specific topic, *the genetics of psychoses*, it has long been apparent that the perennial and at times rather acrimonious "nature-nurture" controversy in relation to the severe types of mental disease has been much more conducive to philological hair-splitting than to real progress. Evidently, a major part of this controversy has been due to incomplete knowledge about the interaction of predispositional, precipitating and perpetuating causes, to many discrepancies between description and interpretation of clinical symptoms indicating behavioral deviation, and to the introjection of varying ideological allergies. It is especially regrettable that this dispute has neither cured a single psychotic patient nor may ever be expected to diminish the vast number of potentially unstable persons, who succumb to the miseries of a severe psychosis in every one year all over the world, irrespective of the political allegiances and preferred philosophical abstractions of the appointed public health authorities in any given country.

One may hope, therefore, that the scientifically unproductive controversy will cease with the final advancement from largely structural or mystically

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[1] This opening address was prepared for presentation at the International Psychiatric Congress (Paris, 1950) where, owing to the writer's inability to attend the meeting personally, it was read by Dr. Eliot Slater of London at the plenary session of the Sixth Section (Social Psychiatry) on September 27, 1950.

sociogenic theories of psychoses to the functional dynamics of a *polydimensional biological concept* with flexible genetic, adaptational and pathoplastic implications and with an interdisciplinary recognition of the adaptive function of life as the starting point for investigations of human behavior disorders. Equally important would be a general acceptance of the fact that the science of medical genetics as an integral part of social psychiatry neither encourages any demagogic schemes advocating the creation or maintenance of special privileges for selected groups of people, nor aims at the introduction of discriminatory standards with regard to available methods of training or psychiatric treatment. Instead, there is abundant evidence substantiating the opinion that an adequate understanding of general genetic principles of human maladjustment will prove to be as indispensable for the *diagnostic*, *therapeutic* and *preventive* purposes of psychiatry as it has been for many other branches of medicine.

The urgent need and general feasibility of a genetically oriented approach to certain clinical problems of psychiatry are particularly apparent in relation to the differentiation of *schizophrenic*, *manic-depressive*, and *involutional* psychoses. With respect to these three important disease groups it is safe to state that preferential inconsistencies in diagnostic classification have been largely responsible for the widespread belief that their symptomatologies are either overlapping or variable expressions of the same basic disturbance. In any case, the frequently reported alternation of schizophrenic and manic-depressive psychoses within individual family units seems to have found its most popular reflection in the rather confusing idea that the children of manic-depressive parents are as likely to be schizophrenic as they may be manic-depressive in turn, while manic-depressive psychosis is very rarely observed among the children of schizophrenic parents. Another theory has been that a manic-depressive patient may become schizophrenic, but that a schizophrenic does not become manic-depressive, presumably because "it is easier to fall down a cliff than it is to fall up a cliff." In some schools, extreme oversimplification of strictly psychodynamic interpretations actually threatened to lead to the relegation of the given psychotic syndromes to the obscure status of "semantic conventions."

However, most of these time-honored theories seem entirely incompatible with the results of our recently completed analysis of the distribution of psychoses observed in 6,115 blood relatives (parents, siblings and co-twins) of a total of 1,232 psychotic twin index cases, that is, of probands distinguished by both their twinning status and verified clinical evidence of a schizophrenic (953), manic-depressive (75), involutional (96) or senile (108) psychosis. This comparative study was based not only on a strictly unselected sample of *psychotic twin patients*, all of whom entered our survey through reports from mental

hospitals to which they had been admitted, but also on a consistently applied system of diagnostic classifications.

In this system, the classification of *schizophrenia* was extended to include the simple, atypical (mixed, diluted) and pseudoneurotic varieties, the acute confusional states precipitated by extreme stress, and the so-called schizo-affective reaction syndrome, in addition to the usual episodic or progressive (deteriorating) types of hebephrenic, catatonic or paranoid coloring, as distinguishable by a disintegrative bend in personality development. The diagnosis of *manic-depressive psychosis* was restricted to cases showing acute, self-limited and unadulterated mood swings of a manic or depressive variety before the fifth decade of life and no progressive or residual personality disintegration before or following psychotic episodes. Reactive or neurotic (situational) depressions were not included in the survey, while primary menopausal and presenile depressions, agitated anxiety states and other non-periodical forms of depressive behavior in the involutional period (50–69) were placed in the category of *involutional psychosis*, together with the typical cases of involutional melancholia characterized by agitated depression with paranoid features. Manifestation of a delusional or depressive syndrome after the age of 70 led to the classification of *senile psychosis*.

The uniform application of this longitudinal scheme of psychiatric diagnoses resulted in the distinct impossibility of finding any pair of *monozygotic* twin partners, whose clinical symptomatology would have warranted their placement into two different diagnostic categories within the range of psychoses studied. Whenever there were diagnostic difficulties with respect to the symptomatology of one member of a psychotic index pair distinguished by monozygocity, they inevitably recurred in the classification of the other twin partner.

In the *dizygotic* sample of index pairs, the only diagnostic discrepancies, overriding the dividing lines between our main groups of psychoses, consist of four opposite-sexed pairs showing varying combinations of schizophrenic, involutional, and senile psychoses. Otherwise, our material offers neither a dizygotic pair with a schizophrenic psychosis in one member and with a manic-depressive psychosis in the other nor a single manic-depressive index family with an authentic case of schizophrenia among the parents and siblings of the index cases.

As a general rule it has been found that the incidence of schizophrenia is increased in the consanguinity of *schizophrenic* index cases, and that of manic-depressive psychosis in the consanguinity of *manic-depressive* index cases, while there is a definite increase in both schizophrenic and involutional psychoses in the consanguinity of *involutional* cases, and a moderate increase in involutional and senile psychoses among the blood relatives of *schizophrenic* cases.

Schizoid personality types are preponderant among the blood relatives of both schizophrenic and involutional cases, but *cycloid* types prevail among the blood relatives of manic-depressive cases.

In addition, age-specific expectancy rates for *involutional* and *senile* types of psychosis follow a sliding scale, which is more or less proportional to the degree of blood relationship to the respective type of index case. It may be assumed, therefore, that monozygotic twin partners are more likely than dizygotic twins or ordinary siblings to be alike in all of those factors which favor the development of an involutional or senile psychosis. Evidently, the occurrence of either type of psychosis not only presupposes the capacity for survival until the later years of maturity and the ability to live through the preceding years without succumbing to any other kind of psychosis, but also requires varying combinations of etiological components, which individually would not be sufficient to produce a psychotic reaction syndrome. The most important causative elements apparently include progressive impairment of physical and mental adaptability, cumulative emotional strain and general insecurity due to increasingly conspicuous signs of aging, and the coexistence of certain basic personality traits such as rigidity, compulsiveness or over-sensitivity, which tend to reduce the adjustive plasticity of a senescent person and, thereby, impair his faculty of adaptation to both involutional changes and senile decrepitudes.

The majority of these traits seem identifiable with *schizoid* personality deviations, although it is probable that some involutional psychoses are actually late-developing and attenuated processes of schizophrenia precipitated only by the impact of involutional experiences. In fact, a few involutional cases may also be related to the emotional vulnerability of cycloid personality types during the period of aging, but no data have been obtained in our studies, which would support a theory of a single-factor type of genetic mechanism producing the ordinary symptomatology of an involutional or senile psychosis.

Consequently, it is indicated by this part of our analysis that the principal genetic relationship of *involutional psychosis* is to the group of *schizoid* personality traits and, therefore, indirectly to the *schizophrenic* disease entity rather than to that of manic-depressive psychosis. Psychiatrically it may be said that the development of an involutional psychosis is precipitated by a strained situation posing a threat of insecurity to the rigid attitudes of a schizoid person with compensatory superiority feelings and a perfectionist self-esteem. Since such persons require an inordinate amount of protection throughout their adult lives, they break down in the involutional period, because they gradually experience an irresistible decline in those resources, which previously facilitated a sufficient degree of adaptation and compensation.

With respect to our remaining two diagnostic categories, *schizophrenia* and *manic-depressive* psychosis, which generally occur before the involutional pe-

riod of life, the available evidence is conclusively in support of specific and basically single-factor types of inheritance. According to an analysis of age-corrected expectancy rates, the chance of developing either psychosis increases strictly in proportion to the degree of blood relationship to the respective type of index case. The corresponding psychosis rates vary from 7.1 to 86.2 per cent in the sibships of schizophrenics, and from 16.7 to 95.7 in the sibships of manic-depressive index cases. The observed frequency of schizophrenia among the parents of our schizophrenic twin probands is 9.3 per cent, and that of manic-depressive psychosis among the parents of manic-depressive index cases is 23.4 per cent.

The balance of evidence concerning the most probable mode of inheritance of the respective main genotypes points to ***recessiveness*** in schizophrenia, and to ***irregular dominance*** in manic-depressive psychosis. There is an increase to 5.0 per cent in the number of *consanguineous marriages* found among the parents of our schizophrenic index cases, but not a single instance of such a mating has been discovered among the parents of our manic-depressive twins. Besides, about 60 per cent of the manic-depressive index cases come from matings between one normal and one manic-depressive or cycloid parent, while the preponderant trend of transmission in schizophrenic index families is in the *collateral* rather than in the *direct* line of descent. The relative *infrequency* of manic-depressive psychosis seems largely explained by factors of selection, which tend to reduce the reproductive rate of the trait-carriers.

Clinically it seems to be of particular significance that the affective instability and biochemical dysfunction produced by the ***manic-depressive*** genotype are apparently correlated with the genetic factors for gout and diabetes and especially with a tendency to *obesity*. If concordant one-egg twin pairs show a definite dissimilarity in the severity of their psychotic symptoms, the display of a milder or more easily controllable manic-depressive syndrome has usually been found by us to be associated with a lesser degree of overweight.

The situation is completely different with respect to the constitutional ability or inability to resist the development, or to counteract the progression, of a *schizophrenic* psychosis. In this group it is the rule that if one twin remains free of schizophrenic symptoms or shows a milder form of the disease than his co-twin, there is always a difference between the twins in regard to physical development, the difference being consistently in favor of the more resistant twin.

Deficient resistance to the effect of the recessive unit factor for schizophrenia is believed by us to be determined by a non-specific and certainly multifactorial type of secondary genetic mechanism. This mechanism is measurable by the capacity for mobilizing effective mesodermal defense reactions and seems to be correlated with the athletic component of physique and with the ability to maintain a stabilized level of body weight.

It is clear that the potentialities of a stable or increasing weight curve as a measurable indicator of the *protective* or *recuperative* powers of a general constitutional resistance mechanism should not be misinterpreted in the sense that merely a gain in weight or excessive overweight might be able to cure schizophrenia. Evidently, the correlated changes in clinical symptomatology and body weight are secondary expressions of basic biological processes which play a role in both phenomena. While some schizophrenics go downhill in spite of, rather than because of, an over-compensatory gain in weight, indicative of a faulty and clinically ineffectual over-reaction, true recoveries do not occur in schizophrenics, who are losing weight, or who prove to be unable to regain weight, lost in the incipient stages of the disease. Therapeutically it may be concluded, therefore, that one of the guiding principles in the management of schizophrenia should be to keep a potential or convalescent patient on a stabilized level of constitutional resistance.

In order to deal efficiently with the genetic aspect of this challenging proposition in relation to schizophrenic and other types of psychosis, it is essential to understand the intricate etiological interaction of gene-specific biochemical dysfunctions, general constitutional (adaptational) modifiers, and precipitating outside factors arising from the effect of certain basic imperfections in the structure of modern human societies. Any approach, which tends to be neglectful of one of these fundamental elements in the causation of a severe psychosis, may be responsible for the crucial difference between therapeutic failure and success.

In conclusion it may be stated that schizophrenia and manic-depressive psychosis appear to be genetically *specific* and genotypically *distinct* disease entities, which are neither interchangeable nor somehow complementary in the genic components of their respective genotypes. There is reason to believe that adequate knowledge of the respective genetic and constitutional background factors of these psychoses will not only be useful in developing a consistent system of diagnostic classifications, but that it may also help in improving the therapeutic, social and preventive management of the various psychoses. Evidently, no factual evidence has as yet been produced to justify the somewhat wishful and potentially dangerous idea that the environmental part in the intricate pathogenesis of a severe psychosis may soon lend itself to a more effective therapeutic control than those functional deficiencies in adaptation determined by genetic elements.

With respect to the clinical understanding and management of those types of psychosis discussed in this somewhat overcondensed report, a concession of our still very incomplete knowledge seems preferable to an attitude of optimistic complacency and, I hope, will prove to be conducive to a *steady progress of psychiatry*.

Heredity in Ankylosing Spondylitis

A Study of Fifty Families

A. H. HERSH, ROBERT M. STECHER, WALTER M. SOLOMON, RALPH WOLPAW AND HARRY HAUSER

Departments of Biology and Medicine of Western Reserve University and City Hospital, Cleveland, Ohio

IN a previous communication Stecher and Hauser (1946) described a pair of brothers with ankylosing spondylitis. Since that time numerous other similar instances have been noted at first hand as well as those reported in the literature, frequently under the synonyms of spondylitis ankylopoetica, spondylitis rhizomelique, von Bechterew's disease, Marie-Strümpell's disease or rheumatoid spondylitis. For convenience the term "spondylitis" will be used to designate the disease throughout this paper, which reports additional families with two or more cases of spondylitis that have been examined by us or have come to our attention, tabulates them along with other instances described in the literature and from the viewpoint of genetics analyzes the 50 sibships studied by the present authors.

In the report referred to above we described two brothers, aged 49 and 47, with spondylitis which began at 23 and 29 years respectively. Two other brothers, aged 28 and 26, with spondylitis, who were described to us by private communication from Reynolds, were recorded. A third set of brothers described by Weil and Allolio (1930), and a fourth set of two brothers found by Ehrlich (1930) in a review of 753 cases were also summarized. Since that paper was published the authors have discovered and examined one additional set of brothers, two pairs of sisters, a father and a son, and finally, a man with spondylitis whose brother and sister have the disease. Through personal communications, data have been received concerning 3 sets of brothers and a brother and a sister from the records of Dr. J. G. Kuhns of the Robert Breck Brigham Hospital in Boston, and of a set of brothers from Dr. C. L. Crang of Ludbury, Ontario.

LITERATURE

The influence of heredity in spondylitis has been discussed by many authors. Geilinger (1918) in a review of the literature found 5 out of 58 patients with von Bechterew's disease and 2 out of 86 patients with Marie-Strümpell's disease had affected relatives. He also described a family of 2 brothers with a maternal uncle, aunt, and grandmother with the disease. In a series of 100 patients Fischer and Vontz (1930) found one family with multiple involvement: a father, two sons, and a grandson. Ray (1931) described concordant male

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twins, aged 31, without mention of the type of twinning. Among 81 patients, Claussen (1937) found a familial incidence in 5 cases, with 8 secondary cases; there was one secondary case in 3 families, 2 secondary cases in 1, and 3 secondary cases in 1 family; one of these instances involved male identical twins, both affected. Scott (1942) in a series of 300 cases, saw family combinations of affected brother and brother, brother and sister, sister and sister, father and son, uncle and nephew, and concordant twins. Stauffer and Moffett (1946) described an affected father, son and grandson, in a four-generation pedigree comprising 27 individuals. Campbell (1947) in a review of 25 cases, stated that two of his patients were identical twins who developed the disease in different countries at the same age. Another two were brothers. A fifth patient had a brother who died with spondylitis and a sixth patient had an uncle and a brother with the disease. Campbell also mentions a family described to him by Wright, including an affected father and son. Rogoff and Freyberg (1948) studied 114 cases and found that 31 patients had involved relatives. One family consisted of 3 affected brothers and an affected father, a second family had two brothers and a son, a third family had concordant monozygotic twin brothers. In the discussion of this paper, Talkov (1948) stated that a familial incidence of rheumatoid spondylitis had been noted in 5.9 per cent of patients having shoulder and hip involvement, and in 2.7 per cent of patients lacking hip involvement. There were 230 patients in his series. Polley (1947), in a series of 1035 patients, noted a woman of 35 with spondylitis who had 3 involved brothers. He also reported two spondylitics each of whom had an identical twin brother who had so far escaped the disease. In discussing Polley's paper, Rosenberger (1948) mentioned 5 sets of involved brothers he had seen. Coste (1947) reported one instance of 2 affected brothers and a father and son. Simpson and Stevenson (1949), in a series of 200 cases, found two men with involved relatives, one a mother, the other a brother.

West (1948) studied 136 cases and obtained family history data for 83 of these. These 83 families contained 95 cases; 73 families had one case, 8 families had two, and 2 families had three cases. Two brothers were involved in 5 families, three brothers in one family, a brother and sister in two families, a brother and two sisters in one family and a father and daughter once. (His article states 83 families had 94 cases, a total differing from the data above.)

Riecker *et al.* (1950) described a remarkable family, kindred 711 from the Heredity Clinic of the University of Michigan. A woman with spondylitis had 13 children. Two daughters and a son had spondylitis and three other daughters and a son had arthritis. A son and a daughter of one of the above spondylitic daughters also had the disease.

The data concerning multiple family involvement with spondylitis which are described above have been assembled in table 1. Sixty-nine families are noted, involving a total of 139 affected individuals. These include 3 pairs of identical twin brothers, two sets of dizygotic twin brothers, 34 sets of 2 brothers, 2 sets of 3 brothers, 5 brother-sister combinations, 3 sets of 2 sisters, 12 father-son combinations. Two brothers and one sister combinations were described 4 times. Mother and son were affected twice, a mother, son and 2 daughters were described once. Combinations of father-daughter, three brothers and one sister, two brothers and two sisters and one brother and two sisters were described once. Two affected brothers also had a grandmother, uncle and aunt affected (Kuhns), two other brothers had an uncle involved, Campbell (1947). An uncle and a nephew were described by Scott (1942) but are not included in the table. Of the 69 families described, 49 had involvement of members of only one generation, 12 had involvement of two generations and three had involvement of three generations. Two families of two generations and one of three generations were comprised of two families listed separately in the tabulation. The secondary index cases in the table all are individuals also listed in the families above. Other instances of multiple

involvement are mentioned in the literature cited but have not been tabulated because details are not available.[1]

A further point may be mentioned in regard to table 1. A glance shows the presence of many more sib-pair than parent-child combinations. Ordinarily such data could be used to make a study of the correlation of age of onset between parent and child for a comparison with a similar correlation between sib-pairs. In many cases in the literature the age of onset seems to be quite uncertain or indefinite. However, the ages of onset for sibs of our own cases are as follows: O. brothers, 19 and 23; F. brothers, 23 and 29; R. brothers, 26 and 28, and a sister 33; H. sisters, 22 and 25; S. sisters, 18 and 18; and T. father and son, 32 and 22. The median age of onset of these 12 sibs was 23.8 years compared to 24.75 years for all the 50 index cases in the series. While too few to make any reliable statistical calculation, these data do indicate a high degree of correlation. This would be expected since sibs are more likely to have subsidiary modifiers in common than parent-child combinations which would be expected to have a lower degree of correlation.

The data of table 1, as suggested to us by Dr. C. W. Cotterman, can be used to test whether the sib-pairs are homogeneous with respect to the sexes. When all sib-pairs are tabulated, excluding monozygotic twins and twins not definitely known to be dizygotic, and then adding the extracted pairs from the larger sibships (e.g., Polley's set of 4 gives 6 pairs, 3 ♂ ♂ and 3 ♂ ♀), the following totals result:

A	Brother-brother pairs	49
B	Brother-sister pairs	25
C	Sister-sister pairs	6
N	Total	80

Since B is approximately twice the geometric mean of A and C, it follows that these 3 numbers giving the various sib-pair combinations approximate a good fit to the binomial $(p + q)^2N$, where p and q are the observed proportions of males and females in all sib-pairs,

$$p = \frac{2A + B}{2N} = \frac{123}{160} = 76.9 \text{ per cent.},$$

$$q = \frac{B + 2C}{2N} = \frac{37}{160} = 23.1 \text{ per cent.}$$

Using the chi-square test we have, with one degree of freedom,

$$\chi^2 = \frac{N(B^2 - 4AC)^2}{(2A + B)^2 (B + 2C)^2} = \frac{80(25^2 - 24 \times 49)^2}{(98 + 25)^2 (25 + 12)^2} = 1.17, \text{ and } P = 0.28.$$

This method shows that the proportion of affected males and females in the entire series of sibships of table 1 are 76.9% males, 23.1% females. But more importantly, the chi-square test indicates to a high degree of probability that the sib pairs are homogeneous with respect to the sexes. This would not be the expected result if some of the conditions reported as spondylitis were due to autosomal factors, others to sex-linked factors. In the latter case we would expect an overloading of brother-brother combinations and such does not occur. This result is in entire agreement with the results of the genetical analysis of the 50 sibships, carried out below. This analysis of all the reported sib pairs as well as the genetic analysis is still unable to say definitely that the autosomal factor involved is the same in all cases. Perhaps the only sure way to such an answer would require an extensive knowledge

[1] Since preparation of table 1 two additional instances of a familial occurrence of spondylitis have come to the authors' attention: Fraser, 1950; Mason, 1950.

TABLE 1. ANKYLOSING SPONDYLITIS IN RELATIVES

AUTHOR	FAMILY NO.	FATHER	SECONDARY INDEX CASE	MOTHER	SON	SON	DAUGHTER	DAUGHTER
Stecher & Hauser	1				x	x		
Reynolds	2				x	x		
Weil and Allolio	3				x	x		
Ehrlich	4				x	x		
Present Study (Hersh *et al.*)	5				x	x		
	6						x	x
	7						x	x
	8	x			x			
	9				x	x	x	
Kuhns (previously unpublished)	10				x	x		
	11				x	x		
	12				x	x		
	13				x		x	
Crang	14				x	x		
Geilinger	15				x	x		
Fischer & Vontz	16				x	x		
	17		F		x			
Ray	18				x	— x		
Claussen	19				x	= x		
	20				x	x		
	21				x	x		
	22				x	x	x	
	23				x	x	x	x
Scott	24				x	— x		
	25				x	x		
	26				x		x	
	27						x	x
	28	x			x			
Stauffer & Moffet	29	x			x			
	30		F		x			
Campbell	31				x	= x		
	32				x	x		
	33				x	x		
	34				x	x		
Wright	35	x			x			

TABLE 1.—*Continued*

AUTHOR	FAMILY NO.	FATHER	SECONDARY INDEX CASE	MOTHER	SON	SON	DAUGHTER	DAUGHTER
Rogoff & Freyberg	36	x			x	x		
						x		
	37				x	x		
	38				x =	x		
Polley	39				x	x	x	
					x			
Rosenberger	40				x	x		
	41				x	x		
	42				x	x		
	43				x	x		
	44				x	x		
Coste	45				x	x		
	46	x			x			
Simpson & Stevenson	47			x	x			
	48				x	x		
West	49				x	x		
	50				x	x		
	51				x	x		
	52				x	x		
	53				x	x		
	54				x	x		
						x		
	55				x		x	
	56				x		x	
	57				x		x	x
	58	x			x			
Tegner	59				x	x	x	
Blécourt	60	x			x			
	61				x	x		
	62		F		x			
	63				x	x		
	64				x	x		
	65				x	x		
	66		F		x	x	x	
	67				x		x	
Riecker, *et al.*	68			x	x		x	x
	69		M		x		x	

Secondary index case indicates an affected sibling taken from the immediately preceding family who serves also as a father (F) or mother (M). Double bar (=) indicates monozygotic twins. Single bar (—) indicates twins which are either dizygotic or of unknown zygosity.

of human chromosome maps based on voluminous linkage data and obviously these necessary data are not available.

With this record, which is far from complete, of multiple involvement of spondylitis in 69 families, it is obvious that the factor of heredity is of much greater importance than two of the present authors had previously supposed.

DATA

The present study is based upon a clinical history, physical examination, and a detailed family history of every case of spondylitis seen by each of us in the past two years. The cases were drawn from the wards or out-patient departments of four Cleveland hospitals, the City Hospital, Mt. Sinai Hospital, St. Vincent's Charity Hospital and Crile Veterans' Hospital, and from private practice. The first affected case in each family was considered the propositus or primary index case. A detailed family history and pedigree was prepared for each patient, particular attention being devoted to the parents and sibs. The number of adult children of the index cases was small and therefore no conclusion could be drawn concerning the occurrence of spondylitis in the children of affected people. Since fully developed spondylitis produces such a clearly defined and characteristic clinical picture which becomes well known to the affected individual, it seemed that his report of the condition of his relatives in this respect would reveal practically all but the earliest and most atypical secondary cases. Nevertheless, the index cases were carefully questioned as to spondylitis, arthritis, rheumatism or crippling disease in their relatives. Affected relatives were recognized promptly by the patient. Twelve of the thirteen cases in 6 families reported here and previously (Stecher & Hauser) were examined by one of us and the diagnosis substantiated.

When individual pedigrees were assembled, the data were transferred to work sheets. Here the data such as present age, sex, diagnosis at age of death, if that had already occurred, were tabulated in columns according to relationship. It thus became easy to determine by inspection the condition regarding each individual family as well as the data concerning all the fathers, the mothers, the brothers or the sisters. All relatives below 20 years of age were neglected.

The study series consists of the families of 50 patients with spondylitis, the index cases. Of these, 46 were men, 4 were women and all were white except for 3 Negro men. The age of onset of their disease ranged from 16 to 52 yr., the mean being 26.22 yr., and the standard deviation 9.1 yr. Information was obtained concerning 47 fathers, 49 mothers, 74 brothers, 62 sisters, 11 sons and 4 daughters. Half of the fathers and mothers, 24 and 26 respectively, 67 brothers, 58 sisters, 10 sons and 4 daughters were still alive at the time the information was obtained. Spondylitis was reported in 3 brothers, 3 sisters and one father, a total of seven times in 247 relatives. The genetic analysis

below is limited to 186 individuals in 50 sibships. These are the 50 propositi, 74 brothers and 62 sisters.

The control series included information on 159 families with rheumatoid arthritis assembled for a study on genetics of that disease, 83 families with Heberden's nodes assembled for an earlier study and previously reported, 96 families, some of which had been studied as controls in the Heberden's nodes studies and additional families of patients seen in the office or dispensaries and found to have none of the diseases under discussion, 43 families of gout patients, the majority of which had been studied and reported previously and 25 families of patients with remote rheumatic fever and rheumatic heart disease. From these 406 index cases in the combined control series histories

TABLE 2. SUMMARY OF STUDY SERIES

GROUP	INDEX CASES	FATHER	MOTHER	BROTHERS	SISTERS	SONS	DAUGHTERS
Study Series							
Spondylitis	50	47 (1)	49	74 (3)	62 (3)	11	4
Control Series							
Rheumatoid arthritis	159	149	152	282 (1)	312 (1)	44	63
Heberden's nodes	83	75	80	125	182	6	10
Control series	96	91	95	152	197	32	13
Gout	43	29	33	65	56	41	45
Rheumatic fever	25	23	23	49	50	28	24
Total controls	406	367	383	673	797	151	155
Cumulative total	456	414	432	747	859	162	159

Total individuals: Study series—297 Control series—2,932 Combined series—3229. Numbers in parentheses indicate affected individuals and are included in the totals.

were obtained concerning 367 fathers, 383 mothers, 673 brothers, 797 sisters, 151 sons and 155 daughters. Ankylosing spondylitis was reported in one brother and one sister, twice among 2526 relatives of the control series. These individuals were sibs of a patient with rheumatoid arthritis and with spondylitis. All three of them, consequently, are also counted in the study series. It is seen, therefore, that spondylitis occurred about 30 times as commonly in the 258 relatives of 50 patients with spondylitis as among the 2526 relatives of the 406 control individuals. This material is summarized in table 2.

At least half of the parents and from one-tenth to one-third of the other classes of relatives were dead at the time of the study. All secondary cases were examined when possible, and in 6 of the 7 recorded instances of ankylosing spondylitis the diagnosis was verified. In the control series, many of the relatives in the Heberden's nodes series and the relatives of about two-thirds

of the control series were examined by one of us (R. M. S.) to verify the presence or absence of Heberden's nodes and note any other obvious rheumatic diseases. The same was true in the gout series because blood was taken from all of the available relatives for serum uric acid determinations.

Since each index case was questioned carefully about the existence in each relative of arthritis, rheumatism, spondylitis or any crippling disease, as well as stiff back, bent back, limping, or joint deformity, the presence of well-developed ankylosing spondylitis which might have existed would have been reported in a large proportion of the affected cases. Any errors of omission were likely to be of about the same magnitude in both series so that the results could safely be compared.

TABLE 3. SEX INCIDENCE OF SPONDYLITIS

AUTHOR	MALES	FEMALES
Scott (1942)	210	90
Fletcher (1944)	36	32
Buckley (1945)	130	20
Polley (1947)	931	104
Coste (1947)	71	1
West (1948)	122	12
Simpson and Stevenson (1949)	158	42
Blécourt (1949)	95	21
Present Series	49	7
Totals	1802	329

DISCUSSION

The present series—counting both normal and affected individuals—is comprised of 120 men and 66 women, a ratio of less than 2 to 1. The preponderance of men is due almost entirely to the fact that 46 of the index cases were men compared to 4 women. Subtracting the index cases from the series, the sex ratio becomes 74 men to 62 women which does not differ significantly from a 1:1 ratio. The sex ratio of affected cases is 49 men to 7 women. Table 3 compiled from 9 published series showed 1802 affected men compared to 329 women, a ratio of 5.2 to 1 in clinic patients. This is no true indication of the sex ratio of cases of all detectable degrees of spondylitis in the general population.

In view of the numerous cases of multiple involvement, there can no longer be any reasonable doubt that heredity plays a major role in the etiology of spondylitis. Physical characteristics occurring at random can be expected to affect several members of the same family according to the law of small independent probabilities in the Poisson distribution. West (1948) has demonstrated that the data on multiple involvement do not conform to that law. In an exhaustive study of the population of Bristol, England, he found among

41,907 families, 74 families with one case of spondylitis, 8 families with 2 cases, and 1 family with 3 cases, compared to 74 with 1, 0.065 families with 2, and 0.00003 families with 3 cases expected on a basis of the Poisson distribution.

The occurrence of spondylitis in both members of 3 sets of identical twins can scarcely be explained on a basis of independent probability. Using West's estimate of an incidence for the disease of about 1 in 2000 for the adult population, the probability of two particular individuals being involved is about 1 in 4,000,000. Since approximately 1 in 90 births are twin births, of which about one-third are identical, involved identical twins could be expected only $1/270 \times 1/4{,}000{,}000$, or once in over a billion population. Assuming that spondylitis is hereditary, one such set of identical twins would be expected for every 540,000 of the adult population. West's estimate of an incidence of spondylitis of 1 in 2000 based on the Bristol population of about 420,000 people would seem to be more reliable than the incidence of 2 cases among 2526 relatives of the control series in the present study. Considering the nature of the computation and the data upon which it is based, the estimates from the two series can be considered to be of a similar order.

Before the mechanism of inheritance can be accurately analyzed certain corrections of the data must be considered. One of these is due to variable age of onset. The question to be answered is how many more cases of spondylitis are likely to develop in the brothers and sisters of the index cases as they grow older. The median age of onset of the 50 index cases in the present series is 24.75 years, the three-quartile age is 30 years, and the age at which seven out of eight of the subjects had developed spondylitis was 33.6 years. Of the 74 brothers, 57, or 78 per cent, are already beyond the age at which seven-eighths of the index cases had developed first symptoms. There were 3 spondylitics among these 57 brothers, or roughly one in 20. Not more than one in 20, or only one, can be expected to develop in the 17 younger brothers. Also, 61 brothers are beyond the age of the three quartile group of whom again 3 are affected, a proportion of one in 20. Since only 13 are below this age, less than one case can be expected to develop symptoms later. Among the 62 sisters, 45 are beyond the age when seven-eighths of the index cases had developed symptoms. Two of these are spondylitics, or one in 22. Of the 17 below this age, less than one case is to be expected. One has been found. It seems likely, therefore, that the finally expected affected among this group of 136 siblings of 50 spondylitics will be 7 or 8 at the most compared to 6 found. However, it might be argued (see Smyth, Cotterman & Freyberg, 1948) that since there is apparently a correlation between the severity of a disease and its age of onset, and since the more severe cases are more likely to serve as propositi, then it might follow that a set of propositi would have an age of onset shifted toward the lower end of the total curve and so lead to an underestimation of

the number of sibs that might eventually develop the disease. Nevertheless, it seems safe in the present instance to make computations using the observed number without correction.

Concerning the problem of the mechanism of transmission it may be said that the family pedigrees show no completely consistent and regular mode of inheritance. The obvious cause of this is that some individuals with a genetic constitution for ankylosing spondylitis develop the condition and some do not. There is a lack of penetrance. It may be recalled that the laws of heredity were discovered by the use of characteristics with full penetrance and that in the first decade or so after 1900, when a new Mendelian ratio could still be exciting, the attempt to have the data on human characteristics fit a known hereditary mechanism often led to the postulation of complex genotypes that were not convincing. This was especially true for those traits in which, as we would say now, the penetrance was different in males and females.

In conditions occurring predominantly in one sex, the possibility of sex-linkage is always suggested. In sex-linkage the gene for the suspected trait is carried on the X-chromosome which males inherit from their mother, and transmit only to their daughters. Fathers do not transmit to their sons. Twelve instances of father-son inheritance and one instance of father, son and grandson involvement are shown in table 1. According to all the data available, spondylitis is not a sex-linked character. Instead, as the analysis will show, it is probably an autosomal dominant with incomplete penetrance, but with a distinctly lower penetrance in females than in males.

With the advances in the genetics of experimental organisms, the concept of penetrance leads to the view that frequently in an apparently irregular and complicated situation, a main gene is involved which is weakly penetrant, but which can be made fully penetrant in a suitable genetic background, that is, with a right combination of genetic modifiers. Even in such weakly penetrant characteristics as the homoeotic mutants of Drosophila, e.g., *podoptera*, Goldschmidt (1948) has found that this mutant can be made 100 per cent penetrant by the accumulation of favorable subsidiary modifying factors. This accumulation in the stock is accomplished by close inbreeding and selection in certain individual lines.

In human genetics it is well known that a dominant gene which lacks penetrance will obviously have the appearance of a recessive in many pedigrees. On the other hand, a pedigree of a recessive that lacks full penetrance would never, as a result of that lack, come to resemble a dominant pedigree. Even in irregularly appearing traits, an occasional pedigree will be found which because of a happy combination of subsidiary modifiers will exhibit complete or nearly complete penetrance. Riecker *et al.* reported such a crucial pedigree of spondylitis with inheritance as an autosomal dominant. Three of 13 children of an

affected mother had spondylitis and two grandchildren of an affected mother were also affected.

Because of the small size of human families, the theoretical proportions of affected to non-affected individuals are not observed. When, as in the present studies, selection of sibships depends upon recognition of an affected sib instead of an affected parent, those families with only normal sibs are not recognized. They must be included if the data are to reveal the expected Mendelian ratios. Correction for this situation can be computed according to the method published by Hogben (1933) and utilized here.

The corrective factor is for characters with full penetrance. If the analysis is in the right general direction, the result can be used to give for the first time an estimate of the degree of penetrance for spondylitis. Table 4 shows that in the 50 sibships composed of 186 sibs,

TABLE 4. COMPARISON OF AFFECTED SIBS WITH THEORETICAL EXPECTATION ON BASIS OF SIMPLE AUTOSOMAL DOMINANT (1:1 RATIO)

Corrected for sibship size assuming complete penetrance. Entire study group included.

SIZE OF SIBSHIP z	NO. OF SIBSHIPS n_z	TOTAL SIBS zn_z	AFFECTED SIBS r	CORRECTIVE FACTORS f	EXPECTED AFFECTED fn_z	VARIANCE s^2
1	3	3	3	—	3.000	—
2	13	26	13	1.333	17.329	2.889
3	9	27	10	1.715	15.435	4.408
4	11	44	13	2.134	23.474	8.604
5	6	30	7	2.581	15.486	6.492
6	3	18	4	3.047	9.141	5.137
7	2	14	3	3.527	7.054	3.334
8	3	24	3	4.015	12.045	5.835
Totals.....	50	186	56		102.964	36.699 $s = \pm 6.$

including the propositi, 102.9 are expected affected compared to the 56 actually found. This indicates a penetrance of 54 per cent. Because of the marked difference in incidence in the 2 sexes, the penetrance for men and for women was computed separately. It was found that 120 or 65 per cent of the 186 propositi and sibs were men and 66 or 35 per cent were women. Of the 103 expected affected sibs in the group, 65 per cent or 67 are therefor expected among the men. Actually, there were 49 affected men instead of 67 expected, indicating a penetrance of 73 per cent. On the other hand, there were 7 affected women instead of 36 expected, indicating a penetrance of 19 per cent. According to these figures, spondylitis should occur in the population in the proportion of 73 men to 19 women. About eighty per cent of the cases will be found in men. This is in the same order as the finding of 87 per cent males in the present series of 2131 cases tabulated in table 3. The estimates of penetrance are of course subject to sampling errors. Using the usual formula ($s = \sqrt{pq/n}$), the standard error for the penetrance in males is ± 4.1 and for females ± 4.8 per cent.

Penetrance in each sex was then computed in a different way, by first dividing the series according to sex of the index case. In this computation some of the families had to be omitted because there was no male index case where only affected women were found in the family

and vice versa. For sibships containing male index cases, table 5 includes 46 families with 115 sibs and 49 affected brothers compared to 71.6 expected, showing penetrance of 68 ± 4.4 per cent. Considering 4 families with female index cases and limiting the computation to sisters alone, we find 6 of 11 sibs affected compared to 6.5 expected or 100 per cent penetrance. These results are obviously higher than are experienced in the general population, particularly in women, and are due in part at least to weighted sampling of the material and elimination of the families with milder involvement. This is indicated by the fact that these two groups include only 125 sibs instead of the 186 sibs in the 50 families. Because

TABLE 5. COMPARISON OF AFFECTED SIBS WITH THEORETICAL EXPECTATION ON BASIS OF SIMPLE AUTOSOMAL DOMINANT (1:1 RATIO)

Corrected for sibship size, assuming complete penetrance. Men only, with at least 1 affected man in each sibship.

SIZE OF SIBSHIPS	NO. OF SIBSHIPS	TOTAL SIBS	AFFECTED SIBS	CORRECTIVE FACTOR	EXPECTED AFFECTED	VARIANCE s^2
1	14	14	14	—	14.000	—
2	11	22	11	1.333	14.663	2.444
3	12	36	14	1.715	20.580	5.878
4	3	12	3	2.134	6.402	2.347
5	5	25	6	2.581	12.905	5.410
6	1	6	1	3.047	3.047	1.379
Totals.....	46	115	49		71.597	17.458 $s = \pm 4.2$

TABLE 6. COMPARISON OF AFFECTED SIBS WITH THEORETICAL EXPECTATION ON BASIS OF SIMPLE AUTOSOMAL DOMINANT (1:1 RATIO)

Corrected for sibship size assuming complete penetrance. Sibships selected because of at least one affected woman but all sibs included.

SIZE OF SIBSHIP	NO. OF SIBSHIPS	TOTAL SIBS	AFFECTED SIBS	CORRECTIVE FACTOR	EXPECTED AFFECTED	VARIANCE s^2
2	1	2	1	1.333	1.333	0.2222
3	1	3	2	1.715	1.715	0.4898
4	2	8	4	2.134	4.268	1.5644
6	1	6	2	3.047	3.047	1.379
Totals.....	5	19	9		10.363	3.6554 $s = \pm 1.9$

of this unusually high penetrance in women correction for small family size was applied to all families with an affected sister and all sibs were included. The result shown in table 6 reveals that 5 families included 19 sibs with 9 affected, compared to 10.3 expected, showing 90 per cent penetrance. Having regard to the standard error, this may be taken as indicating perhaps a complete penetrance. In sibships with a woman affected there is a stabilizing influence on the main factor resulting in a higher than ordinary penetrance. This penetrance will be discussed later. Despite the complete penetrance seen in those sibships with an affected woman, penetrance in women in the entire series was low, only 7 of the 67 women or 9 per cent were affected compared to 49 of 120 men or 41 per cent.

The lower penetrance in women probably depends upon the "buffering" action of the additional X-chromosome, an effect not only of the X-chromosome, but of other parts of the genome. This is a principle which has been reasonably well established in experimental organisms. The X-chromosome is thought to contain secondary modifiers which "buffer" the effect of the defective gene and impair its influence. The offending gene in such a heterozygous female would still be passed on to one-half of her children, some of whom may be unfortunate enough to have modifiers which would stabilize the effect of the gene for spondylitis. At the appropriate age these children would be affected with the disease. On the other hand, the children who inherited the gene but at the same time inherited a set of modifiers favorable to overriding the effect of the main gene would be non-spondylitic.

TABLE 7. COMPARISON OF AFFECTED SIBS WITH THEORETICAL EXPECTANCY ON BASIS OF SIMPLE RECESSIVE (3:1 RATIO)

Corrected for sibship size, assuming complete penetrance. Entire study group included.

SIZE OF SIBSHIP	NO. OF SIBSHIPS	TOTAL SIBS	OBSERVED AFFECTED	CORRECTIVE FACTOR	EXPECTED 3:1 RATIO	VARIANCE s^2
1	3	3	3	1.000	3.000	—
2	13	26	13	1.1428	14.8564	1.5919
3	9	27	10	1.2973	11.6757	2.3667
4	11	44	13	1.4628	16.0808	4.6206
5	6	30	7	1.6389	9.8334	3.5507
6	3	18	4	1.8248	5.4744	2.3279
7	2	14	3	2.0196	4.0392	1.9405
8	3	24	3	2.2225	6.6675	3.5168
Totals.....	50	186	56		71.6274	19.9151 $s = \pm 4.46$

The above analysis assumes that the offending gene is dominant and that the matings in most of the cases were between one parent who was heterozygous for spondylitis and the other homozygous for the normal allele. The contrary hypothesis that the main gene for spondylitis is the recessive one and that the normal allele is dominant was then tested. It must then be assumed that both parents in practically all cases would be heterozygous and the ratio of expected progeny would be 3 normal to 1 spondylitic. Table 7 shows that 56 sibs are affected compared to 71.6 expected. This indicates penetrance of 78 per cent compared to 55 per cent found when the condition was considered as a dominant. Computing penetrance for the sexes separately, it is shown that 65 per cent of 72 expected affected or 47 men, compared to 49 found for 100 per cent penetrance. Conversely, there were 7 affected women compared to 25 expected, showing penetrance of 28 per cent in women. These figures indicate that spondylitis should appear in the general population in the proportion of

47 men to 25 women or that 65 per cent of all cases will be found in men compared to 80 per cent in the hypothesis of dominance and 85 per cent found in table 3. It is clear that these results based on the analysis of spondylitis as an autosomal recessive trait is contradictory to the obviously low penetrance and besides would require an exceptionally large reservoir of heterozygotes in the general population. As indicated above it seems clear that the data are more consistent with the conclusion that spondylitis is due to an autosomal dominant factor.

In the study of human heredity it is becoming more widely appreciated that the analysis of pedigrees and the conclusion drawn from the statistical tests made on the accumulated data need to be reasonably consistent with the gene frequencies in the population. It is difficult to achieve this desirable result because many human traits commonly show a lack of penetrance of the genes involved and there are few characteristics for which the incidence in the general population is very accurately known. This is also true of spondylitis, but it is nevertheless desirable to attempt the gene frequency analysis.

Apparently the most satisfactory data on the incidence of spondylitis are those of West, who found 1 in 2000 in the adult population of Bristol, England. He also found a ratio of 10 men to 1 woman with spondylitis. Consequently there are 10 men and 1 woman with spondylitis in every 22,000 of the adult population.

Because of the fairly large number of reported instances of spondylitis in 2 and 3 generations, this low incidence of 1 in 2000 of the adult population is itself evidence that spondylitis is a dominant trait. If it were a recessive, some slight excess of parental consanguinity would be expected in the 50 index cases. None was found.

For determining the gene frequency one needs an estimate of the penetrance as well as the incidence of the condition in the population. The two different estimates of the penetrance in men of 73 $\pm$ 4.1 per cent and 68 $\pm$ 4.4 per cent are in fair agreement so that a round figure of 70 per cent may be taken as the penetrance in men. The estimate of the penetrance in women is somewhat less certain. From our small sample the penetrance in women was 19 $\pm$ 4.8 per cent. But in these families, as argued above, the penetrance is greater than in the general population. We may make another estimate of the penetrance by subtracting the 4 index cases which leaves 62 women only 3 of whom have spondylitis, where on the basis of a 1:1 ratio 31 would be expected. This gives a penetrance of about 10 per cent in women. This is in good agreement with West's census of the total population of Bristol who found a ratio of 10 men to 1 woman for a penetrance of 7 per cent. Consequently for the calculation of gene frequency 70 per cent penetrance in men and 10 per cent in women will be used.

Assuming the trait to be an autosomal dominant, and making the calculation

first for men, then, with 70 per cent penetrance, one man in 1540 of the population will have a genetic constitution for spondylitis. The incomplete penetrance lowers the incidence among men in the population to 1 in 2200. With random mating of a population in genetic equilibrium the homozygous dominants, the heterozygotes and the homozygous recessives are present in the population in the relative frequencies $d^2 + 2dr + r^2 = 1$, where d is the frequency of the dominant factor for ankylosing spondylitis and r is the frequency of the recessive normal allele. The calculation shows that for men the value of d is 0.00032 and for r the value is 0.99968, and so consequently the frequency of heterozygotes $2dr$ is 0.00064.

If the trait is an autosomal dominant there are as many women as men with the genetic constitution for spondylitis, so that these gene frequencies should be very similar to those obtained from the corresponding calculation from the data for women. Again on the basis of West's figure the incidence of women in the adult population is 1 in 22,000, but allowing for the low penetrance, taken as 10 per cent, the frequency of women in the population with the genetic constitution for spondylitis becomes 1 in 2200. The calculation from the equation for a population in genetic equilibrium gives 0.00028 for the frequency of d and for r the value is 0.99972, consequently $2dr$ is 0.00056. Considering the approximate character of the incidence and the uncertainty in the value of the penetrance, these two values for the frequency of men and women with a heterozygous constitution for spondylitis, namely 0.00064 and 0.00056, are in quite close agreement. In fact rounding the figures to the 4th decimal place gives exactly the same value, namely, about 6 in 10,000 have a heterozygous genetic constitution for ankylosing spondylitis. The gene frequency d is so low that for the present discussion the probable incidence of homozygous dominants d^2 in the population may be neglected.

The most plausible, but nevertheless still tentative, conclusion from the analysis of the data, is that ankylosing spondylitis is due to an autosomal dominant factor which has about 70 per cent penetrance in males and perhaps about 10 per cent or slightly greater penetrance in females. This conclusion is quite consistent with the analysis by inspection of significant pedigrees, with a numerical test on pooled data and with the estimated gene frequency in the population.

There is a further peculiarity, in regard to the difference in penetrance between males and females, which is interesting in itself and which may become of considerable importance in the further study of human genetics, especially if it should prove to be of common occurrence. It seems that in sibships containing an affected woman there is a stabilizing effect of the main factor and penetrance is higher than the average in such families. Penetrance was found to be nearly complete in the 5 sibships containing an affected female in the present series. In the kindred described by Riecker *et al.* the affected

grandmother had two affected daughters and an affected son among a total of 9 daughters and 4 sons. West found that 4 of 10 affected women had affected brothers.

A similar phenomenon is observed in the genetic analysis of hyperuricemia, in which the autosomal dominant gene is 84 per cent penetrant in men and about 12 per cent penetrant in women. The ratio of about 7 to 1 is of the same order of magnitude as that in ankylosing spondylitis. A pedigree of hyperuricemia in which three women were affected (see fig. 2, Stecher, Hersh and Solomon, 1949) also showed well the stabilizing effect on the action of the gene and so increased the penetrance in the set of families. Several other families as indicated in the above mentioned paper were also found.

The cause of the higher penetrance in families where the mother is the affected parent is not known, but there are several known mechanisms from the genetics of experimental organisms which at least are possibilities also for human genetics. These possibilities are (1) plasmagenes, (2) a maternal effect on the egg cytoplasm, (3) some peculiarity during intra-uterine development, and (4) simply a chance combination of subsidiary modifying factors, i.e. the genetic background. These possibilities are not all equally plausible. Since the first three of these are relatively rare, so far as known at present, while the fourth is of common, indeed almost universal, occurrence, it seems that the most antecedently probable mechanism involved is that of subsidiary modifying factors which in some way is related to the functioning of the two X-chromosomes in the female parent as against the single X in the male parent. There are no doubt other possibilities which in the present state of knowledge are even more speculative, e.g., an effect of the heterochromatin. There are no data available at present to distinguish between these several possibilities in the case of spondylitis.

What is known about the genetics of spondylitis leaves open the further question concerning the physiological and metabolic pathways through which the main gene operates or how the modifying factors might act to override these effects in some cases, that is, to lower the penetrance, or on the other hand, to accentuate the effect in other cases. In gout it is now known that the predisposing genetically controlled condition is hyperuricemia (Smyth, Cotterman & Freyberg, 1948; Stecher, Hersh & Solomon, 1949) and in this case the blood serum uric acid is higher in males than in females. The query naturally arises in regard to ankylosing spondylitis whether some similar condition of the organism or a more local property of the tissues concerned might be involved. After discussing several investigations along this line, West seems to make out a fairly good case that hyaluronic acid and hyaluronidase might play the requisite role.

This view is strengthened by the report of Paff and Seifter (1950) whose investigations indicate that hyaluronidase may be an active factor in normal

bone formation, and also by the report of Shifrin, Keller and Simpson (1950) that hyaluronic acid appears to be related to the laying down of fibrous connective tissue. But this problem calls for considerable caution. It cannot be immediately assumed that hyaluronic acid or hyaluronidase plays a role in ankylosing spondylitis that is analogous to the role of hyperuricemia in gout.

From a biochemical point of view, a mutant must produce either a substance which is lacking in the normal or more of a substance than is produced in the normal, or the reverse, that is, the mutant may produce less of a substance or be totally lacking in a substance produced in the normal. Now it happens in experimental forms that for the cases which are known the mutant is defective in a substance which is present in the wild type or normal. In humans it is known that in diabetes, an hereditary disease, insulin is lacking but this brings on a hyperglycemia. In gout, hyperuricemia is present but somewhere there is a lack which somehow allows this increase in blood serum uric acid, but what the deficiency is in this case is still not certainly known. And so in the case of ankylosing spondylitis, it may well be that a change in hyaluronic acid and hyaluronidase may be the consequence of an antecedent deficiency in ACTH or some other substance which is genetically controlled.

SUMMARY

Heredity plays an important role in the etiology of ankylosing spondylitis as shown by the numerous reported cases of multiple involvement in sibships and at least 3 pairs of concordant identical twins. The analysis by inspection of significant pedigrees and numerical tests on pooled data lead to the conclusion that ankylosing spondylitis is due to an autosomal dominant factor which has about 70 per cent penetrance in males and about 10 per cent or slightly greater penetrance in females. Taking West's estimate of an incidence of one case in 2000 of the adult population, gene frequency analysis reveals about 6 heterozygotes per 10,000 population, in both sexes.

In sibships containing affected women there is a stabilizing effect upon penetrance making it almost complete in both sexes; this seems to be especially the case when the mother has ankylosing spondylitis.

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